Approaching the 21st Century: Opportunities for NIMH Neuroscience Research

National Institute of Mental Health

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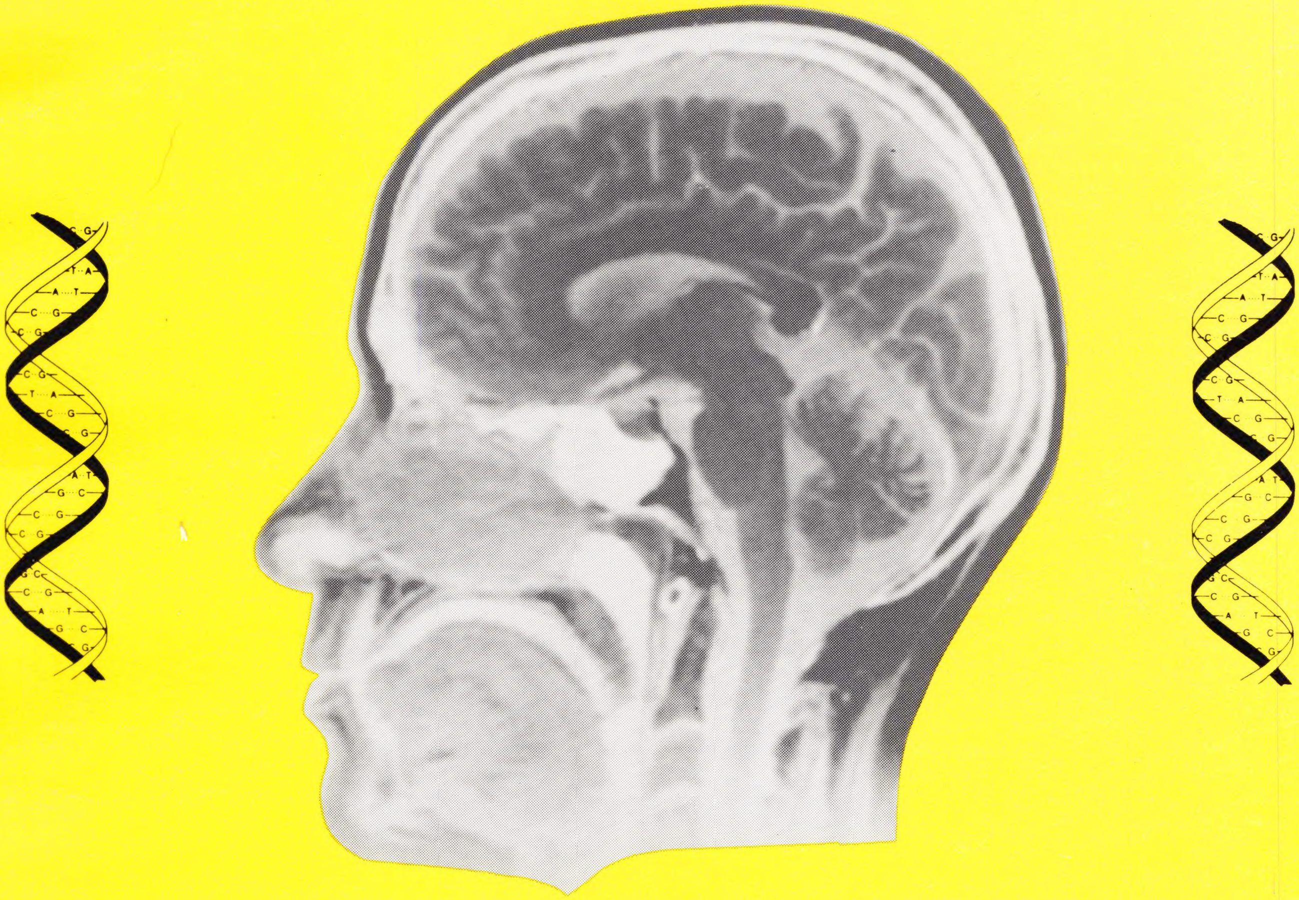

The National Advisory Mental Health Council Report to Congress on the Decade of the Brain

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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5600 Fishers Lane
Rockville, Maryland 20857

This report is the result of deliberations conducted by the National Advisory Mental Health Council (NAMHC) and contains recommendations designed to assist in guiding national strategies aimed at the amelioration of mental health problems. These recommendations, therefore, reflect the professional judgement of the NAHMC and do not necessarily reflect Administration policy.

Library of Congress Catalog Number 88-601969
DHHS Publication No. (ADM) 89-1580
Printed 1988, Reprinted 1989

EXECUTIVE SUMMARY

The National Advisory Mental Health Council (NAMHC) is pleased to submit this report to Congress on the opportunities for advances in the clinical and basic neuroscience of mental illnesses, as requested by the House Appropriations Committee in its FY 1988 budget for the Department of Health and Human Services.

As we approach the twenty-first century, we are on the brink of discovering the biological basis for many of the major mental illnesses and the impact of the environment on their course. We will be able to design better drugs for their treatment, and ultimately to prevent such devastating diseases as schizophrenia, depression, anxiety, and manic-depressive disorders. Through neuroscience research, we can realistically anticipate a time in the near future when we will fully understand our brains—how they function and dysfunction. However, we still have a long way to go, and the powerful new research approaches being developed are expensive—though not as costly as the problems they can help us resolve.

The staggering costs of mental illness and behavioral disorders in our country are well known to Congress. The burden of caring for those with chronic mental illness threatens to exceed the capacities of many communities. Now Alzheimer's disease and dementia associated with AIDS are adding another layer of expense. The costs of acute care for mental illnesses are rising astronomically, and no one can measure the cost to society of learning disabilities among our youth, eating and sleeping disorders, and other behavioral dysfunctions.

The cost in human suffering for both victims of mental illness and their families cannot be described to those who have not experienced this pain. Mental diseases affect 15-20 percent of the American public annually, with no regard for age, social status, race, or religion. Although these illnesses can result in suicide or accidental death, in most instances they are not fatal, but rather lead to a lifetime of suffering, helplessness, and distress for the victims and their families.

Now is the time for Congress to insist on a concentrated effort in neuroscience research on mental illnesses. A lesson can be taken from the history of Federal funding of biomedical research. The tremendous support for biomedical research in the early 1970s led to the current medical advances in treatment and prevention of heart and vascular diseases, cancer, endocrine and dietary diseases, and inborn errors of metabolism. The lesson here is that typically 10-15 years elapse before the knowledge of basic science directly benefits the American public.

We are poised for neuroscience breakthroughs in the 1990s that will generate clinical successes during the twenty-first century. The pace of this progress ultimately depends on adequate Federal funding. The

direct benefit to the country of such an investment would be the return to society and the workforce of many of the millions of mentally ill Americans. The financial gain would be billions of dollars annually, but the most important benefit would be in the improved quality of life for these patients and their families.

In the last two decades, we have made gains in treating mental disorders and have developed drugs that ameliorate some of the symptoms of affective illness, schizophrenia, and anxiety. But we have found no cures, and we still do not know how these disorders originate. However, in the last 10 years, neuroscientists have made major breakthroughs in their understanding of normal and abnormal brain processes. In fact, 95 percent of what we know about brain function was discovered during this period.

This report focuses on the potential increase in our knowledge base to be gained through clinical neuroscience studies using molecular genetics approaches and brain imaging (positron emission tomography, magnetic resonance imaging and spectroscopy, neuromagnetic imaging, and brain electrical activity mapping). Improved treatments will result from extending current research on the mechanisms of brain action of psychoactive agents and the molecular modeling of newer agents through computer-assisted drug design. Neural transplantation studies and improved animal models that reflect the major symptoms of human illnesses are additional approaches with great promise.

Advances in clinical neuroscience are critically intertwined with the continued accumulation of knowledge obtained through basic neuroscience research. This report details the quantum leaps now possible through enhancement of research on the following:

- Brain development and the multitude of trophic factors necessary for normal brain function
- The neurochemical and structural changes that accompany learning and memory processes
- The molecular mechanisms through which the individual neurons in the brain act in concert to perform the symphony of normal human behavior
- The anatomical connections of discrete groupings of neurons that are primary in producing emotions, cognition, attention, and other discrete behaviors, both normal and abnormal
- The neuroendocrine and other hormonal systems and their regulation of brain function, as well as brain regulation of these endocrine systems
- The possible role of neurotoxins in brain disorders and their use in research on brain function
- Computer modeling of brain circuitry and testing of nonlinear dynamic theories of brain mechanisms

- The brain and immune system interactions and how they relate to behavior
- Genomic regulation of brain function and the genetic underpinning of behavior
- The neurobiology of circadian rhythms

In all these areas, researchers are using the latest technology on subjects ranging from invertebrates to humans.

Now we face an epidemic of AIDS, with its accompanying depression and dementia. Along with the major national programs aimed at attacking this virus, NIMH is vigorously pursuing research to understand and ameliorate its central nervous system effects, as well as to develop better interventions and educational approaches toward preventing its spread in the general population.

The NIMH is also inaugurating a National Plan for Research on Schizophrenia to attack this particularly devastating and mysterious illness. This plan has been under development for more than a year and will soon be presented to Congress. A major enhancement of the neuroscience research effort at NIMH will greatly augment the Schizophrenia National Plan as well as provide answers to many of the other disabling mental illnesses.

To take advantage of the unique opportunities available today, the NAMHC recommends initiating the Decade of the Brain by increasing the FY 89 and FY 90 NIMH budgets for neuroscience research as follows. The total for new investigator-initiated grants should be increased to $54 million, and $30 million should be appropriated for new research centers in each year. Funds for new instrumentation, laboratory renovations, and adequate animal facilities are needed totaling $32 million per year; appropriations for Research Scientists Awards and the training of new scientists should be increased by $10 million annually. In addition, the NIMH budget for contracts related to neuroscience activities requires an estimated $7 million each year. The intramural research budget requires $3.6 million to launch several new initiatives and $90 million for the construction of a neuroscience research center (Building 49). To ensure that the goals of this report can be achieved, the operational budget needs to be increased to provide for an expansion of the Institute neuroscience extramural staff by 35 and the intramural staff by 20, along with sufficient operations support.

The neuroscience effort to date has brought us to the threshold of fully comprehending the most complex and important organ—the human brain. Congressional support of this endeavor will revitalize the interest of our brightest young people in scientific careers and, together with the existing pool of talented, energetic scientists, provide answers to questions that have been pondered for centuries. Now, in our lifetime, we have a unique and tantalizing opportunity within our grasp.

A CHALLENGE FOR NEUROSCIENCE:
50 Important Questions to Answer in the Decade Ahead:

1. What are the fundamental mechanisms controlling the synthesis, release, storage, and inactivation of endogenous neuroactive molecules?

2. How do environmental factors, such as stress or experience, alter brain structure and function?

3. What neurochemical alterations contribute to the etiology and pathophysiology of mental illness?

4. How do membrane-bound molecules, such as proteins, phospholipids, and glycolipids, influence nerve function?

5. How do psychotherapeutic drugs exert their action?

6. How are memories encoded, stored, and retrieved?

7. How does neuronal activity influence genomic expression of nerve cells?

8. How are the neuronal receptors and ion channels structured and regulated?

9. How can we create functional connections between artificial microcircuits and the nervous system?

10. How do viruses affect nerve function?

11. What role do viruses play in mental illnesses?

12. How does synaptic activity alter the excitability of receptors, making them either more or less responsive to stimuli?

13. Do endogenous or exogenous neurotoxins play a role in the etiology of mental illnesses?

14. What are the molecular and cellular mechanisms of circadian rhythms?

15. What causes undifferentiated cells to form neurons?

16. How is the correct wiring of the brain achieved?

17. Once neuronal connections have formed, what are the specific trophic factors necessary for their maintenance or alteration?

18. Do any mental illnesses result from inappropriate neuronal connectivity or organization?

19. What is the purpose of normal nerve cell death during brain development, and what are the controlling factors?

20. What are the determinants of nerve cell death in normal aging, Alzheimer's disease, and other dementias?

21. Can trophic factors be used to enhance brain nerve cell regeneration or prevent their degeneration?

22. What are the significant structural and functional changes in the frontal cortex and subcortical structures in schizophrenia?

23. What are the substrates and dynamics of postreceptor intracellular signaling?

24. What are the detailed neuronal systems mediating basic drives and experiences such as pain, pleasure, attention, and emotion?

25. Can we develop useful data-based computer models of the brain?

26. Can transgenic animal models be developed for mental illnesses?

27. What are the neural substrates of higher cognitive properties of the human cerebral cortex?

28. What essential properties of the brain give rise to conscious awareness?

29. How do cellular and molecular operations of neuronal systems produce individual differences in behavior?

30. What is the function of sleep, and how is it regulated by the brain?

31. What factors account for the lack of complete concordance for major psychiatric diseases in identical twins?

32. Why is thinking so easy for normal people and so aberrant in schizophrenics?

33. How does the endocrine system influence the brain and behavior?

34. How does circadian system dysfunction result in behavioral or physiological disorders?

35. Is bright light a practical treatment for nonseasonal depression, premenstrual syndrome, sleep problems, and mood problems of the elderly?

36. What are the neurobiological factors underlying the gender differences in incidence and treatment responses in mental illnesses?

37. What approaches can be used to replace neurons lost in patients with neurodegenerative diseases?

38. What determines if more than one neurotransmitter is used by a specific neuron?

39. What are the functional consequences of cotransmission?

40. What new insights into brain function and human behavior can be gained through the application of nonlinear dynamic theory?

41. What biological measurements are useful in diagnosing subtypes of mental illnesses; serving as guides for successful therapeutic intervention; or predicting illness in advance of clinical symptoms?

42. How do physical illnesses cause psychopathology, and what is the brain's role in producing physical illnesses?

43. How are the functional interactions between brain and the immune system mediated?

44. Can pyschoneuroimmunological approaches be developed as therapeutic interventions?

45. Can therapies be developed to prevent mental functions from deteriorating in the aging population?

46. What advances in mathematics, physics, and computer science can be used to enhance noninvasive brain imaging techniques?

47. What neurobiological factors contribute to nonresponsiveness to psychotherapeutic drugs?

48. What genetic defects result in mental illness?

49. How can the genetic machinery of the brain be manipulated to alleviate mental illnesses?

50. Given the degree of homology between the human brain and those of other species, what makes us unique?

CONTENTS

INTRODUCTION

Neuroscience and Mental Health

This report encapsulates the field of neuroscience research and its potential contributions to the achievement of the National Institute of Mental Health (NIMH) mission. It is another step along a road predicted with increasing emphasis and precision since the NIMH 5-Year Research Task Force of 1975, the Report of the President's Commission on Mental Health of 1978, and the Office of Technology Assessment's Report of March 1984, "Impacts of Neuroscience." Recently (1984), the NIMH initiative culminated in a comprehensive evaluation and planning document, "The Neuroscience of Mental Health." Each of these reports precisely defined the onslaught of new methods, new data, new concepts, and new grounds for linking and probing normal and diseased brains, as well as the implications of these new insights for a wide range of nationally important problems ranging from education and psychosocial interactions through the identification, diagnosis, and prevention of psychiatric disorders.

Today, we stand on the brink of discovery, and the need for knowledge has never been greater. The media are filled with reports of teenage suicide, widespread eating disorders, drug and alcohol abuse, the waste of learning disabilities, the sorrow of Alzheimer's disease, and the panic of AIDS. The homeless are everywhere, and many of them suffer from mental illnesses. Depression is now recognized as a major problem for our growing elderly population, and may be one of the most common ailments at any age.

In 1988, the direct cost of clinical care for an estimated 40 million American victims of psychiatric disorders is expected to be in excess of $40 billion. Yet careful studies show that only 20 percent of persons with mental illnesses are in treatment. Maintaining the chronically mentally ill puts a heavy financial burden on the community, the State, the criminal justice system, and the Federal Social Security system. Many believe that psychiatric disorders have been too long ignored by both medical and political agencies and deserve a very high research priority.

This report describes the recent advances made by neuroscientists in their search for the causes of mental illnesses, effective treatments, and cures. It also indicates the accomplishments that can be anticipated over the next 5 to 10 years if research is allowed to proceed at the most efficacious pace.

Neurosciences: The Growth of a Discipline

Neuroscience represents a fusion of several scientific disciplines—biophysics, biochemistry, physiology, anatomy, pharmacology, and

psychology— all focused on acquiring an ultimate understanding of the relationships between brain and behavior. As an independent investigative discipline, neuroscience is relatively new, originating in the 1970s. The remarkable growth of interest in the field is reflected in the burgeoning membership of the Society for Neuroscience, which rose from about 250 charter members in 1971 to more than 11,000 members today.

The mounting number of scientists seriously engaged in this field has produced an even more rapidly expanding body of factual and conceptual information about the brain. One crude measure of this information explosion can be found at the National Library of Medicine, where nearly 100,000 publications in the archives contain the term "brain" in their titles, more than double the number of such articles 5 years ago. This broad base of knowledge has significant implications and analogies for ongoing work in other research areas as well.

These new observations are even more exciting and heuristic because they derive from advances in a wide variety of newly developed research methods. The improved analytic power, namely the ability to ask questions and get rigorous data to generate and test hypotheses, not only further fuels the rate of information acquisition, but just as significantly improves the value of the observations to the field. The result is a broadly based scientific discipline, moving forward rapidly, and continuously producing new insights into the nature of the brain's functions and, importantly, into the nature and causes of the still poorly understood disorders of the brain and behavior. To appreciate the latter aspect fully, it may be valuable to review the characteristics of neuroscience research and their relevance to mental illnesses.

Levels of Neuroscience Research

Neuroscientists conduct their research at several levels, ranging from studies of molecules through analyses of social interactions. Within the major levels, large series of question-asking strategies operate horizontally to further define the important elements in the brain and their mechanisms of interaction and regulation. Transcending each level of research is a vertical strategy that employs the thread of specific molecules (in a bottom-up strategy) or specific behaviors (in a top-down strategy) to link, through specific cells in specific ensembles of interacting cells, the complete set of characteristic elements and interactions that are needed to explain, understand, and predict the operations of the normal and pathological brain. Each level of resolution can be considered as an independent, freestanding field of exploration.

Molecular Neuroscience Research

At the molecular level, scientists seek to identify all the important molecules involved in operations of the brain. Research in the past

decade has largely emphasized molecules that are critical for communication between neurons, such as the neurotransmitters, their receptors, and the varying array of molecules associated with transmitter synthesis, storage, release, and response.

Neuroscientists are trying to determine how many kinds and types of neurotransmitters there are. The several different chemical classes of transmitters known today range from simple small molecules such as amino acids and monoamines to more complex forms such as neuropeptides, steroids, and lipid mediators of cell-cell messages. In one class, the neuropeptides, more than 100 chemical transmitters have already been identified, with new ones being added continuously.

Another important example of the growth in this field is the ability today to specify the actual amino acid sequences of neurotransmitter receptor proteins. As a result, it is possible to discriminate amongst the varieties of receptors, distinguish those that directly regulate ion channels from those that employ more complex mechanisms of signal transduction, and—critically—to define the sites at which the endogenous ligands activate the receptor, thus providing a natural template for rational drug design.

In addition, new molecular genetic strategies seem likely to provide the basis for linking gene expression to specific molecules. Two particular areas of molecular discovery may be anticipated: (1) improved identification of the intracellular structural proteins that allow the adult nervous system to attain, maintain, and adjust its functional connectivity and (2) further identification of "growth factors" that normally either initiate or prevent repair and plasticity responses.

The major advances incorporated into the findings that generated these concepts lead, in turn, to a still more general and perhaps more profound index of our remaining ignorance of the brain: How many genes (and gene products) are made by the brain? Current research would place this number at well over half the genome, and perhaps as many as 30,000-50,000 genes, of which fewer than 1 percent can now be specified.

Nonetheless, the discovery of the first molecular genetic linkages for specific psychiatric disease states is at hand. Finding a DNA molecular sequence that correlates with a specific psychiatric diagnosis, however, is but the beginning of the quest for the biological basis of that disease's diagnosis, treatment, and prevention. Experiments showing the molecular nature of affective disorder and schizophrenia are exciting to scientists and nonscientists alike because they support the long-held realization that these diseases have a biological basis. But establishing a genetic linkage to psychiatric disease is a long way from obtaining biological insight into that disease. That factual connection must ultimately be built in terms of the cells that express the normal or abnormal genes, the means by which the specific gene product

participates in brain cell functions, and the manner in which the altered gene manifests specific functional alterations to produce the signs and symptoms of the disease.

Cellular Neuroscience Research

The growth in factual information at the cellular level, largely gleaned from the brains of small experimental animals, may be viewed as the leading edge of the neuroscientific information explosion. These studies hold considerable promise for understanding the normal and eventually the pathological human brain as well.

At the cellular level, scientists examine the degree to which cell classes in the brain can be characterized as to their shared and unique properties, and how these cell classes interact in circuits or ensembles of two or more neurons to accomplish functions generally referred to as information processing. The human brain contains an estimated 100 billion neurons, but no one is willing yet to guess how many kinds of neurons exist. Traditionally, neuroscientists have divided them into specific classes based on their shape (pyramidal, mitral, stellate, etc.), their size (magnocellular, parvocellular), their location within the brain (cortical, spinal, thalamic, etc.) or in specific functional systems (motor, sensory, etc.), or their transmitter type (GABA-ergic, noradrenergic, cholinergic, etc.). Clearly, none of these features per se is an adequate index, since any given brain cell has qualities on each of these lists.

Building on the new waves of specific genetic information, future categorizations should be based less on these qualitative phenotypic designations and more precisely on the molecular designations of their specific genetic categorizations. This information may help determine why certain nerve cells are susceptible to certain degenerative or infectious agents that other neurons are able to resist, and why some damaged nerve cells, even within the brain, are able to repair themselves while others die.

Two of the major avenues of advances on the cellular level in the past decade have been (1) the ability to define neuronal circuitry experimentally by microscopic anatomical methods and (2) the ability to define the transduction mechanisms of interconnected neurons through neurochemical analysis of specific transmitters and receptors. The study of cell-cell interactions, whether synaptic transmission between connected neurons, or the poorly understood areas of neuron-glial interaction, will surely benefit from the molecular discoveries.

Supracellular (Behavioral) Neuroscience Research

Research at the supracellular level examines the integrative phenomena that link populations of neurons, their supporting glia, and vasculature into ensembles specialized for performing particular behavioral tasks. These studies also examine the brain's ability to monitor internal

chemical signals and, thus, to provide regulatory responses over virtually all internal visceral systems, including specifically the endocrine, cardiovascular, gastrointestinal, and genito-urinary system.

Recent advances in identifying neurotransmitters and their receptors have led to the suggestion that neuronal events may also regulate the immune system and alter its ability to respond to self and to foreign invaders, such as cancer or AIDS-promoting viruses and other infectious agents. Verification of these concepts would clearly broaden the domain of the brain's responsibilities to include not only all the diseases within the fields of psychiatry and neurology, but internal medicine and its subspecialties of allergy and infectious diseases; cardiovascular, gastro-intestinal, and metabolic disorders; and reproductive physiology.

Research at the behavioral level has the greatest relevance to the mental health sciences because it seeks specifically to understand the basis for the behavioral functions of the brain. Such work extends from the complex but still poorly understood mechanisms of learning, to the far less well conceived functions that underlie much more complex mental phenomena such as attention, emotion, language, and abstract reasoning.

Studies at this level, in both experimental animals and man, have traditionally sought to analyze the operational rules governing information processing and emotional reactivity within individuals, and the degree to which inter-individual behavioral responses may be predicted. Recent thrusts at this level of analysis have begun to exploit the growing base of biological (i.e., anatomic, biochemical, and pharmacologic) information, to perturb and manipulate the brain, and thus to gain insight into the mechanisms regulating these behavioral events in order to understand their dysfunction in mental illness.

This field has gained further momentum through the development of noninvasive functional tests that enable researchers to identify, in normal and patient samples, the sites that are altered in prolonged states of functional activity (i.e., vigilance, sleep, complex mental tasks) or psychiatric phenomena (such as hallucinations, delusional depression, or mania). The noninvasive imaging and assessment strategies have also helped identify the sites at which hallucinogenic or psychotherapeutic drug molecules may act. Although the latter tests have not yet provided absolute diagnostic nosology, nor specifically linked discrete neuronal ensembles to specific disease states, such insights are destined to emerge from the present momentum.

Opportunities and Needs

Neuroscientific research today has become very expensive: teams of researchers employ expensive instruments and use rare and expensive resources (animals, cells, chemicals, and computers) to operate their

research and training programs at near maximal capacity. Over the past decade, the average cost of funded grant projects has steadily increased. Unfortunately, the funds added by the Congress for the support of neuroscientific research within NIMH has not kept pace with the growth in the number of well-trained investigators, their well-regarded ideas, or their highly qualified research proposals.

These conclusions are borne out by the fact that while the number of grants funded has increased, the proportion of high-priority approved grants that are unfunded has also increased, and the average priority score that can be paid has been pared sharply. To exclude these potentially important opportunities means to forego the potential breakthroughs they may have uncovered.

Congress must realize that while the costs of the neuroscientific efforts described here are high, they pale when compared to the costs of the disorders they hope to alleviate. In FY 1987, the NIMH neurosciences research budget (approximately $30 million) averaged 75¢ per patient, or $1 in research for every $3,000 these disorders cost. The Institute of Medicine's 1985 Report indicated that a substantial increase in the NIMH research budget could be easily justified considering the costs of these disorders to society, the relative expenditures in other less burdensome disorders, and the availability of well-trained scientists and well-founded research proposals. Compared to research on other leading diseases that impose far less chronic burden on our population, research within the psychiatric and related disciplines affected by the neurosciences remains seriously underfunded.

Perhaps it is appropriate now to do more than simply bear passive witness to the progress that has been obtained despite the vagaries of budgetary ups and downs and to consider ways to accelerate the ultimate results that might now be gained. The time and methods may now be at hand to begin to consider implementation of one or more large national programmatic research campaigns of coordinated research. This report presents plans for the development of specific programmatic initiatives in several specific directions, such as enhancement of the National Brain Bank Programs, revitalization of the needed instrumentation base, and strengthened support for several different aspects of computer-assisted sciences.

The key to future realization of the undoubted linkages between human genetics and human brain and behavioral disorders must be an emphasis on the continued resolution and refinement of details on the cells and circuitry operations of the brain. Another programmatic initiative, the development of a National Data Base of Neuronal Circuitry, is proposed as a first step in organizing the existing information on neuronal circuitry, neurotransmitters, their receptors, and their functions. This leads to a second step, the recognition that investigator-initiated neuronal circuitry research may be overlooking large regions of human and nonhuman primate neuronal circuitry whose details may be important to the eventual understanding of psychiatric disorders. A

national program to provide these details could be envisioned given the current availability of well-trained scientists, sensitive methods, and a means to integrate the new data into the existing data bases. Such an effort could lead to a detailed map of specific gene products, specific transmitter molecules and their receptors, specific cell types, specific cell circuits, and specific behavioral functions in the primate brain, with direct extrapolations testable in the human. With these points in mind, the reader will unquestionably find the chapters that follow both intellectually rewarding and a basis for continued support.

Additional Reading Materials

General Neuroscience

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THE IMPACT OF MAJOR MENTAL ILLNESS ON SOCIETY

Scope of the Problem

The major mental illnesses are among our society's most urgent health problems. The disability, chronicity, and social stigma associated with psychiatric disorders exact a personal, familial, and economic toll that is unsurpassed by any other contemporary medical or social problem in the United States. In 1988, major mental illnesses are expected to affect *more than 40 million Americans* and cost *in excess of 40 billion dollars* in direct clinical care, with the expected losses in indirect costs being *greater than 50 billion dollars.*

Psychiatric disorders within the NIMH mandate include schizophrenia, affective disorders, the many forms of senile and presenile dementia including Alzheimer's disease, the anxiety disorders, the spectrum of childhood disorders, and the variants of eating and sleeping dysfunctions. To this list must also be added brain dysfunction, behavioral abnormalities, and dementia (that resembles Alzheimer's disease) accompanying the onset and course of Acquired Immune Deficiency Syndrome (AIDS), our most recent national health epidemic.

Each of these illnesses represents a complex interaction of biological, psychological, and social variables. They affect both genders, every age group, and every social and racial stratum of our society. No other group of disorders has such pernicious and long-term consequences, nor is any other group of disorders as widely distributed across different sectors of our population.

Findings of epidemiological studies designed to identify the number and distribution of major mental disorders in the United States paint a grim picture of the problem confronting our mental health researchers, practitioners, and administrators. We now know that the aggregated rate of mental disorders for children, adults, and the elderly exceeds 20 percent of our population annually, with most cases associated with depression and anxiety diseases or substance use disorders.

At any given moment, mental disorders account for the majority of patients receiving clinical and hospital care in the United States today. Yet research shows that only one-fifth of those identified as having a mental illness are currently under treatment. Many of our nation's street people—as well as countless numbers of youth, immigrants, refugees, substance abusers, and isolated elderly—do not seek assistance. The potential, therefore, for greatly increased treatment costs is real and staggering unless research breakthroughs leading to treatments, cures, and prevention are fostered.

The Major Mental Illnesses

Schizophrenia.—Schizophrenia, a group of illnesses of unknown origin, is found in approximately 1 percent of our nation's population per year. Schizophrenic disorders typically begin in the early teens or young adulthood. They are characterized by a broad spectrum of symptoms including, but not limited to, disordered thought, social withdrawal, hallucinations, delusions, and bizarre behavior. There is no known cure, and the disorders tend to be progressive across a person's lifetime. However, antipsychotic drugs in combination with active psychosocial and behavioral rehabilitation have been successful in limiting personality disintegration and in promoting some behavioral competence. Approximately 40 percent of all hospitalized psychiatric patients in the United States suffer from schizophrenic disorders.

Affective Disorders.—The affective disorders comprise a group of mood dysfunctions and illnesses that include the extremes of elation and despair. While some individuals suffer from deep depressions, others undergo periods of excessive elation and uncontrolled energy (mania). For some, these extremes alternate in a repetitive cycle. In all instances, the person's intellectual, emotional, occupational, and social functioning are greatly disturbed. Depression produces such a profound feeling of hopelessness that suicide is sometimes seen as the only escape. In fact, a substantial proportion of the approximately 29 thousand Americans who kill themselves each year suffer from an affective disorder.

While the risk of anyone developing a major depression in one year is about 6 percent, most human beings experience significant transient depressive episodes, making depression one of the major mental health problems in the world. New medications combined with new forms of psychotherapy (e.g., cognitive psychotherapy) have made depression highly responsive to treatment. New research is being directed toward understanding the genetic aspects of depressive disorders and the biological and psychological measurement of different subtypes of the affective disorders.

Dementias and Alzheimer's Disease.—The dementias constitute a broad spectrum of biopsychological diseases and dysfunctions associated with recognizable changes in the structure and function of the brain and nervous system. These diseases and dysfunctions can result from injuries to the brain and nervous system caused by accidents, strokes, toxins, nutrient deficiencies, and genetically related metabolic disorders.

A growing number of dementias arise from abuse of alcohol, heroin, amphetamines, marijuana, or cocaine. Some of these disorders result from chronic abuse while others develop from extreme doses and impurities in the drugs. One tragedy of the severe drug problem in our nation is the mounting number of youths who consequently face a lifetime of disability and impairment.

Alzheimer's disease is characterized by progressive brain deterioration resulting in memory loss, disorientation, depression, and confused and bizarre behavior. The patients eventually reach the point where they can no longer talk, walk, or think effectively and decline to a nonfunctioning vegetative state and eventually death.

Alzheimer's disease and other dementias currently affect approximately 3 million people. More than half the nursing home beds in the United States are occupied by victims of Alzheimer's Disease and other dementias, and at least twice as many are being cared for by families outside of institutions.

Acquired Immune Deficiency Syndrome (AIDS).—AIDS has been called the modern-day Black Plague. More than 50,000 cases had been reported by January 1988; more than 50 percent of these individuals are now dead, including approximately 80 percent of those diagnosed before 1985. As many as 1.5 million people are carriers of the AIDS virus. They are currently asymptomatic but will soon begin to evidence AIDS symptoms. Another 200,000-400,000 persons are estimated to be suffering from AIDS-Related Complex (ARC) disorders.

One of the most tragic aspects of the AIDS epidemic is the growing number of infected children. Thus far, 563 cases of pediatric AIDS have been identified; two-thirds of these children have died. Ninety percent of infected newborn children are born of black or Hispanic mothers.

AIDS is caused by the Human Immunodeficiency Virus (HIV), which interferes with the body's ability to resist disease by destroying the immune responses of the body to foreign bacteria and viruses. As the immune system breaks down, the AIDS victim sickens and eventually dies. Homosexual and bisexual men are at greatest risk for HIV infection. Users of intravenous drugs are the second largest group of individuals infected with HIV. A small minority of victims acquire AIDS through blood transfusions and heterosexual activity.

Most AIDS patients develop a primary infection of the central nervous system resulting in both intellectual and behavioral deficits, including memory loss, dementia, depression, personality change, and bizarre behavior. The relationship between the immune system and behavior has become an important area of research, called psychoimmunology or behavioral immunology. Some surprising new discoveries have been made on the relationship between behavior and the production of antibodies, hormones, and other immune system protective mechanisms.

Anxiety Disorders.—Ten percent of the American population develop anxiety disorders annually. This group of disorders includes phobias (i.e., irrational fears), panic attacks, obsessive-compulsive disorders, and other fear and tension syndromes. They are characterized by intense feelings of anxiety with accompanying physiological problems such as dizziness, muscle tension, heart palpitations, and gastrointestinal dysfunctions.

Childhood and Adolescent Disorders.—Scientists estimate that about 12 percent of all children and adolescents suffer from various mental disorders that severely impair their intellectual, emotional, social, and familial functioning. A broad spectrum of these disorders is associated with prenatal and birth dysfunctions resulting in hyperactivity, oppositional behavior, and social withdrawal. With the rise in family relationship and substance abuse problems, depression and suicide are increasingly prevalent among children and adolescents. Learning disabilities, such as dyslexia and attention deficits, are also found across a sizable sector of our youth. For some disorders, medications, special education, behavior modification, and family therapy are effective therapies.

Eating Disorders.—The eating disorder anorexia nervosa affects approximately one in 100 teenagers, primarily females. Anorexia nervosa is characterized by a relentless pursuit of thinness. Anorexics will not eat, and in many instances, use diuretics and laxatives to lose weight. They frequently lose more than 25 percent of their body weight. Yet, no matter how thin they become, the individuals still feel that they are overweight.

Bulimia nervosa is another eating disorder found predominantly in young women. Approximately 4 percent of the adolescent population are affected, with a higher percentage found among young adults. This illness is characterized by episodes of binge eating and self-induced vomiting. Bulimics often suffer bouts of depression. They are often difficult to identify because they may not evidence weight loss. Individual and group psychotherapy in combination with antidepressants and antianxiety medications have proven moderately effective in treating the major symptoms, but a more enduring cure eludes discovery.

Sleep Disorders.—Disorders of sleep afflict an estimated 20 million individuals in the United States. Such disorders range from uncontrolled daytime sleep (narcolepsy) and dysfunctions associated with sleep (nocturnal myoclonus, sleep apnea) through abnormalities in initiating and maintaining sleep (insomnias). Sleep disorders are also common in rotating-shift workers, resulting in a disrupted circadian timing system. This disruption and resultant sleep deprivation can produce decreased vigilance, automatic behaviors, and personal injury, posing safety hazards for workers and, in many cases, for the public as well.

The Cost of Mental Disorders

Estimates based on reported cases show that the mental disorders described above will affect more than 40 million Americans in 1988. The economic cost for those who receive clinical or hospital care will exceed 40 billion dollars; the loss in economic productivity may well exceed an additional 50 billion dollars. NIMH's carefully conducted

Epidemiological Catchment Area studies showed that only one-fifth of those identified as having a major mental disorder were currently being treated. When unidentified cases are included, the major mental disorders are clearly our nation's number one health problem. Research on the causes, treatment, and prevention of major mental disorders deserves to be one of the highest priorities in our national health budget.

Today, largely because of federally funded research and training programs, we have a new and better understanding of the causes and treatment of many forms of depression, anxiety, and acute psychotic disorders. Children's disorders, including learning disabilities and behavioral adjustment problems, are being redefined and reconceptualized, and we are gaining new insights into the mechanisms by which sleep and eating disorders develop and are maintained. We have also made progress in understanding the genetic and neurochemical bases of Alzheimer's disease and related forms of dementia.

This report provides substantial evidence of the specific progress made through NIMH-supported research. We have produced significant gains in our knowledge of the epidemiology, diagnosis, treatment, and prevention of the major mental disorders. Current and new research projects will enable us to answer many questions about the etiology and treatment of these disorders within the next decade.

Given the magnitude of the problem we face and the toll it exacts on our nation's health and well being, we cannot stop now, so close to the answers. The personal and economic costs of the problems we face today because of mental illnesses are so vast that immediate, expanded support for our research, training, and prevention efforts must be given the high priority it deserves.

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PROSPECTS IN CLINICAL NEUROSCIENCE:

Potential for Alleviating Mental Illnesses

The ultimate goal of neuroscience research sponsored by NIMH is to understand the workings of the human brain in sufficient detail to effectively treat or prevent the broad variety of behaviorial disorders and mental illnesses, ranging from learning disabilities to schizophrenia. Recent developments in the more clinically oriented neuroscience research—studies with human subjects or having direct impact on human health—have brought us significantly closer to this objective. Sophisticated new techniques and intriguing new findings promise major achievements over the decade ahead.

Finding the Roots of Mental Health Problems

Molecular Genetics

Heredity plays a key role in etiology of mental disorders.

One of the most consistent findings about major mental illnesses is that they run in families. While environmental elements may play a role in producing similar behaviorial dysfunctions among close relatives, several lines of investigation show the importance of inheritance. Children born to parents with schizophrenia, affective disorders (manic-depressive illness), alcoholism, or anxiety, personality or learning disorders have an increased likelihood of developing the same disorder—even if they are reared from infancy by normal adoptive parents. Identical twins (genetically the same) are more likely to have the same mental disorder than are fraternal twins.

Overt mental health problems are not the only behaviors tied to the genes. Studies of twins have shown that individual differences in personality are about 50 percent heritable, indicating that genetic factors work together with social and environmental influences to make us who we are. Since about 60 percent of the genetic information contained in the human genome is used only in the brain, the causes of many behavioral disorders may have at least some footing in the genes.

Until the advent of modern molecular biology, scientists were limited in their exploration of the link between inheritance and illness. Today, neuroscientists are using the powerful tools of recombinant deoxyribonucleic acid (DNA) technology to search for the genetic errors that lead to mental illness. Just 4 years ago, investigators accomplished the remarkable feat of locating the gene for Huntington's chorea in a tiny region on chromosome 4. More recently, they pinpointed the position of genes for neurofibromatosis, familial Alzheimer's disease, and manic depression.

Genes are key to deciphering molecular basis of illnesses.

Once identified as related to an illness, the gene can serve as a "Rosetta stone" to decipher the molecular basis of that illness. Scientists should be able to determine what protein the gene creates, and this should help identify the biochemical abnormality producing the symptoms of the disease, ultimately leading to correction of or compensation for the defect.

Finding the gene.—With few exceptions, the nucleus of every cell in the human body has 46 separate structures called chromosomes composed of DNA. Along these chromosomes lie the genes, the basic units of heredity. DNA is the genetic material—the blueprint of each individual—carrying all the information needed to produce the proteins and other chemicals that make up the specific body. This information is coded in the sequential arrangement of the thousands of pairings of the four nucleotide bases of which DNA is made. The order of the genes, the gross arrangement of these nucleotides, does not seem to vary much in humans; the nucleotide sequence within a given gene, however, can vary somewhat without substantially affecting gene function.

Genetic errors or mutations that produce disorders are most commonly found by searching not for the abnormal gene itself, but for markers in the DNA—signposts that point to the abnormal gene—because much more DNA surrounds a gene than is in the gene. This approach, used so successfully with Huntington's disease, is called linkage marker analysis.

Restriction fragment length polymorphisms are markers for the genes of mental illness.

Finding linkage markers depends on locating what molecular biologists call restriction fragment length polymorphisms (RFLPs), minor variations present throughout human genetic material that can be detected by the action of enzymes—restriction enzymes to be exact. Dozens of restriction enzymes have been identified. Each one splits the DNA string wherever it finds a specific sequence of nucleotides, called restriction sites, which are typically four to eight nucleotides long. The resulting fragments of DNA can then be separated according to their size. The number of pieces depends on how many restriction sites exist in the DNA; three sites will result in four fragments, ten sites in eleven fragments, and so on.

When a restriction site is altered, the restriction enzyme will no longer cut the DNA there, and one less piece appears when the fragments are separated. The altered site, together with the segments of DNA immediately surrounding it, is the restriction fragment length polymorphism. Researchers sample the DNA of large families looking for polymorphisms that are always present in the DNA of those family members affected by the disorder of interest and never present in those not afflicted. Such a marker is said to be linked to the disease—the disease gene and the marker lie so close on the chromosome that they are likely to be inherited as a genetic unit.

When a familial disease is linked to a genetic marker, it is assumed that a gene predisposes to the illness. This conclusion is important, because

many psychiatric diseases are familial, but not everyone accepts their genetic basis. Once the region of interest is identified, it can be progressively narrowed by finding additional DNA markers until the disease gene is identified and cloned. Researchers have already accomplished this feat with the genes causing Duchenne's muscular dystrophy and cystic fibrosis.

In some cases, neuroscientists have reason to suspect a particular gene, and that gene is then used as the marker. Candidate genes are chosen on the basis of either their function or location. The gene for the enzyme tyrosine hydroxylase, for example, is a strong candidate in manic-depressive illness. It maps to the same region as the disease gene in the Amish family (see below), and the enzyme is involved in the biosynthesis of neurotransmitters thought to be important in manic-depressive illness.

If a candidate gene turns out to be the disease gene, it will be linked to the disease in families, and affected individuals will have an abnormal genetic code in the DNA comprising that gene. Therefore, the candidate gene approach complements the linkage marker strategy by providing the next link in the causal chain that will lead to the source of the disease itself.

When a candidate gene or restriction fragment length polymorphism is identified, neuroscientists can prepare radioactive DNA probes that, when added to a sample of DNA, will stick to the sample wherever the exact matching nucleotide sequence exists. If a probe binds to an individual's DNA, it shows that the marker is present in that person's genes. DNA probes are therefore useful in genetic counseling. In fact, such a test now exists for people at risk for Huntington's chorea, which presents its first symptoms when its victims are in their 40s. Developing such diagnostic and predictive tests for mental health disorders will be one of the major achievements for molecular biology in the near future.

Manic-depressive illness.—The most striking results in clinical neurosciences research using genetic approaches have been obtained in bipolar manic-depressive illness. Two different linkage markers were identified in the past year.

Gene marker proves manic-depressive illness is genetic and pinpoints disease-causing gene.

In the first instance, an Old Order Amish community cooperated for several years with investigators doing diagnostic studies (linkage studies) of their large families. In such communities, where people are well known to their associates, manic-depressive illness has long been recognized as being "in the blood," i.e., inherited. Thus, the Amish fully appreciated the importance of the study. They willingly provided blood specimens that were used to establish cultures of their white blood cells, providing an immortal and renewable source of DNA for RFLP analysis.

In 1986, molecular genetic studies showed that one gene that causes the illness in one Old Order Amish kindred is located at the tip of the

short arm of chromosome 11; the specific gene and gene product are currently being identified. The first enzyme in the pathway for the synthesis of dopamine (tyrosine hydroxylase) was first considered to be the susceptible gene because it lies close to the linkage marker on chromosome 11. However, some recent experiments suggest that this is unlikely. Research is currently underway to "walk" closer to the gene.

Another study, relating the inherited traits of color blindness and blood glucose-6-phosphate dehydrogenase enzyme activity, showed a close linkage of these traits to the inherited pattern of manic-depressive illness in certain families. The genes for these traits are known to be localized on the X chromosome, precluding father-to-son transmission of mania in these families. The exact localization of the gene is under study through DNA RFLP analysis.

Linkage studies place Alzheimer's disease gene on chromosome 21.

Alzheimer's disease.—Investigators have found a few families in which Alzheimer's disease appeared to be transmitted as a single gene. These observations provided both a limited region of the genome and ideal families in which to look for the disease gene. A search for linkage turned up the expected disease gene and localized it within a small region on chromosome 21.

Neuroscientists knew, too, that large numbers of plaques containing the protein amyloid form in the brains of Alzheimer's patients. The procedure for identifying and cloning the gene coding for a specific protein is straightforward. So while some investigators were conducting linkage studies, others were cloning the gene for amyloid protein. To the surprise of everyone, the amyloid gene was found on chromosome 21 in the same region as the gene causing familial Alzheimer's disease. Initial excitement over the amyloid protein gene in Alzheimer's disease was premature. Recent studies have shown that this gene is not abnormal in Alzheimer's disease, although disturbances in its regulation may still be a factor.

Future benefits.—Neuroscientists are using the molecular genetics approach with a number of major mental illnesses. Over the next 5 years, they should complete a genetic map of all the human chromosomes, complete with the location of restriction fragment length polymorphisms and specific genes, making it much easier for other researchers to pinpoint the location of a disease-causing gene. Even as this document was being written, two laboratories reported that they had found markers, and prepared the corresponding gene probes, spanning about 95 percent of the human genome. Before long, a number of genes responsible for mental illness should be identified, and research should progress quickly into finding the biochemical roots of mental illnesses.

An important byproduct of identifying the genes connected with various mental health problems will be the ability to study how factors outside the body interact with these inherited characteristics to produce illness. Armed with gene probes, researchers will be able to identify those

individuals within the same family who are carriers of the defective gene and those who are not. By contrasting those at-risk persons who actually develop the disorder with those who do not, researchers will be able to identify the role of other causative factors—high stress situations, alcoholism, etc.—that might be avoided by lifestyle changes, much as persons at genetic risk for heart disease can lower their risk by increased exercise and lowered cholesterol intake.

Functional and Structural Brain Imaging

The human cerebral cortex is responsible for those higher mental processes that give us our very humanity. It is also the site of many behavioral problems. The intricate workings of the cerebral cortex have remained unknown, in part because of their very complexity, in part because the brain is encased in a bony fortress that shields this delicate organ from harm.

Until recently, scientists had to rely on autopsy studies to search for physical and biochemical abnormalities in human patients who had suffered from mental health problems. Today, several types of brain imaging techniques make it possible to pinpoint such changes in living, thinking, behaving subjects, often before any abnormal behavior is apparent. Together, these techniques offer a promising opportunity to study the highest cognitive functions of the intact human cerebral cortex.

New imaging techniques allow exploration of higher cognitive functions in living humans.

Positron emission tomography.—Physiological, biochemical, and pharmacological processes can be quantitatively measured in the living body by an imaging technique known as positron emission tomography (PET). Subjects are administered trace amounts of biologically active natural compounds or drugs that are labeled with a radioactive isotope. These compounds distribute themselves throughout the brain according to their biochemical roles, and the radioactivity emitted is recorded by a tomographic scanner. These cross-sectional images, created through computer reconstruction, are essentially biochemical maps that enable us to make simple measurements of brain function in living organisms, including humans, while the subject or patient is behaving normally or demonstrating the signs and symptoms of a given disorder.

PET provides biochemical maps of the living brain.

The radioisotopes required for PET studies decay to nonradioactive forms in a matter of seconds or minutes. This minimizes any radiation exposure of the subject. However, the short life of these isotopes requires that they be made in a medical cyclotron at or near the site of the imaging study. Thus, a typical PET installation has both the PET scanning device and a cyclotron to produce the isotopes that a waiting chemist uses to synthesize the labeled natural compounds or drugs.

The brain is undoubtedly organized into functional neural networks that must, by virtue of their complexity, be highly integrated, change dynamically under different conditions, and be altered by disease

PET visualizes neural circuits of specific behaviors.

states. PET provides the opportunity to see these networks in action. Researchers can examine subjects in different behavioral states, e.g., lying still during the initial study, then performing any number of motor, sensory, cognitive, or memory tasks—moving a finger, listening to music, and so on. The changing patterns of the distribution of the isotopes indicate the biochemical processes and neuronal networks involved in those tasks.

Researchers have known for some time that nerve cells communicate with one another using receptor systems, and within the last 4 years, they have been able to see neurochemicals bind to receptors in a living subject by using PET. Their progress has unequivocally demonstrated the ability not only to image the distribution of major neurotransmitter receptors in living human brain, but also to quantitatively determine the number and biochemical characteristics of these receptors.

Studies of normal behavior in volunteer subjects have shown the visual, auditory, motor, and sensory networks in action. For example, visual stimulation increases brain metabolism in the appropriate visual centers in proportion to the frequency and complexity of the stimuli used. Auditory signals activate the left and right hemispheres of the brain differentially: verbal stimuli tend to cause responses in the left hemisphere of right-handed individuals, while nonverbal stimuli produce the opposite result. Subjects' prior experiences may be important in how their brains perceive these types of stimuli—experiments showed that professional musicians or individuals that used highly stereotyped and analytical approaches when listening to music tended to activate their left hemisphere while less experienced or nonanalytical listeners tended to activate their right hemisphere.

PET indicates where learning occurs in the brain.

PET techniques have allowed investigators to observe the process of learning. Individuals performing a task use certain regions in the cortex to control the necessary movements; these areas show up nicely in the tomograph. If the task is very overlearned—signing one's name, for example—more primitive structures are activated as well as the cortex. Thus, learning a motor task may cause the induction of or additions to a neuronal network in different brain regions. When disease affects these more primitive brain areas, the cortex appears to reestablish control over the task, allowing the skill to be maintained. This compensatory mechanism has its price, however. The subjects with the disorder cannot perform the task in an automated and overlearned way, but must concentrate on what they are doing. Such findings have implications for the rehabilitation of patients after acute brain injury or in identifying underlying and basic mechanisms that the brain uses to compensate for ongoing degenerative diseases.

PET demonstrates what drugs do in the living brain.

PET provides the first opportunity to examine drug action and pharmacology directly and dynamically in the living human subject in conditions of both health and disease. Two strategies have been used to gain insights into the mechanisms of drug actions and therapeutic

outcomes. In the first, therapeutic doses of drugs are administered to patients and PET measurements obtained before and after treatment with tracer amounts of biologically active compounds that determine blood flow, metabolism, or other natural processes in the brain.

The second strategy is to add a radioactive tag to the drug itself. This approach reveals the actual concentrations of the drug in different brain regions, and these findings can be correlated with therapeutic effects in different disease states. For example, a population of patients with a psychiatric disorder is considered for evaluation with drug X. After 3 months of therapy, 10 percent of the patients improve on this drug regimen. Clinically, the drug would be considered only minimally useful in treating this disorder and probably abandoned. However, for the 10 percent that responded, the drug may have been of major benefit. By labeling the drug and imaging the subjects in a PET device, different biochemical characteristics of the brains of the individuals who responded might have been identified. Thus, PET could be used to pharmacologically classify patients with behavioral, neurological, or psychiatric disorders and to guide therapy by providing individually specific pharmacologically relevant drug treatment categories.

Within the next few years, PET will help neuroscientists identify a biochemical signature for each mental health disorder, as well as the subtypes of that disorder. PET studies of patients with panic and obsessive-compulsive disorders have provided initial insights into areas that may be affected by these disease processes during their symptomatic phases. Such studies have revealed altered blood flow and glucose metabolism in certain brain regions; these results are guiding further explorations into determining the underlying basis and strategy for treatment of these often incapacitating behavioral syndromes.

Schizophrenia is a disorder that affects thought processes. Studies with PET allow the opportunity to observe changes in the biochemical networks of the brain in both medicated and unmedicated patients. The vast array of symptoms that schizophrenic patients may manifest and the different categories of disorders found among schizophrenic patients make this a challenging area for future PET research.

In addition, the technique will enable researchers to determine the effects of various therapies, both biological and behavioral, for each patient. By identifying neuronal networks that are altered by disease processes and reestablished by behavioral therapy, PET may provide important insights into the mechanisms by which behavior modifying therapy induces treatment success in patient groups. A byproduct of this approach will be a guide to improving behavioral therapies and rehabilitation strategies for patients with psychiatric disorders.

In short, the long-term applications of PET to behavioral and psychiatric disorders will undoubtedly result in a wide range of new insights into the fundamental processes of brain function and alteration of that

function by disease states. Biochemical assays of neuronal systems will become commonplace. Presymptomatic detection of psychiatric disease will be routine. Selection of therapy and followup of patients will be commonly handled using these assay techniques.

Magnetic signals of brain show neural processes of cognition.

Neuromagnetic imaging.—Another recently developed technique, neuromagnetic imaging, noninvasively records the weak magnetic signals produced by electrical activity in the human cerebral cortex. These signals are undistorted by the skull, making it possible to measure the electrical signs of human cognition, or thought, and to accurately localize their sources within the brain. Early experiments using this new technique were aimed at identifying neural signals associated with the activity of the primary sensory areas, the gateways by which the human cerebral cortex gains access to the outside world. These investigations were strikingly successful: researchers were able to record neural signals from outside the head while preserving information about their intracranial location. In this way, investigators mapped the human somatosensory (touch) and visual cortices, charting the path that incoming nerve signals took in these parts of the brain. These studies also showed that the auditory cortex is organized according to frequency, that is, different parts of the auditory cortex respond to nerve signals generated in the ears by specific frequencies of sound. In addition, spoken language and other auditory information appear to be processed in separate areas of the brain.

Neuromagnetic methods have also been used to map and localize magnetic signals generated by electromagnetic discharges in patients with epilepsy caused by localized brain damage. In many cases, these spikes were produced by the same abnormal brain tissue responsible for the epileptic seizure. It soon became clear that neuromagnetometry could noninvasively locate certain types of abnormal epileptic brain tissue, thus aiding the surgical treatment of selected seizure disorders.

To locate the neural currents connected to human thought processes, it is necessary to plot the magnetic field produced by such currents versus their distribution over the surface of the head. These magnetic measurements are made using a neuromagnetometer, a device containing a number of sensitive magnetic sensors called SQUIDs, short for Superconducting QUantum Interference Device. Today's SQUIDs function only when cooled to the temperature of liquid helium, making neuromagnetometers expensive and bulky. However, recent developments in superconductivity research promise warm-temperature SQUIDs that would revolutionize the neuromagnetic study of human thought by providing a large number of relatively inexpensive magnetic sensing channels. With the widespread availability of more powerful multiple-channel neuromagnetometers mounted in special magnetically shielded chambers, a whole new category of behavioral investigation will be possible: the study of the complex brain anatomy of human thought as it occurs.

Magnetic resonance imaging.—In sharp contrast to neuromagnetic

imaging, which measures magnetic fields originating in the brain, magnetic resonance imaging (MRI) uses imposed magnetic fields to study brain anatomy. These magnetic fields, generated by large superconducting magnets, may be several trillion times greater in strength than the magnetic emissions of cerebral neurons. Nevertheless, MRI technology poses no known harm to subjects, and they can be tested repeatedly without fear of any adverse health effects.

Magnetic resonance imaging pictures brain in exquisite detail.

The images generated by magnetic resonance technology are unsurpassed in anatomical detail, and they reveal minute changes that may occur with time. Thus, the technique offers the ability to detect previously unrecognized changes in the brain, and will almost certainly provide additional information about known abnormalities. Perhaps more importantly, though, magnetic resonance imaging will increase our knowledge about when structural abnormalities first appear in the course of a disease, how they affect subsequent development, and precisely how their progression or evolution correlates with the mental and emotional aspects of the disorder. Not only will this greatly increase our understanding of diseases, but by integrating information gained from different disorders we will better understand the way that emotion and cognition change in a normally functioning brain.

MRI indicates structural abnormalities in brain of schizophrenics, autistic children, manic-depressives.

Although MRI has been available for clinical studies of psychiatric patients for only a few years, several important observations have already been made. For example, MRI examination of the brains of schizophrenics suggest that the cerebral cortex, particularly the frontal lobes, may be reduced in size. The shape of the corpus callosum, the link between the two halves of the brain, may also be abnormal in some schizophrenics. These early findings suggest that some alteration, possibly during the brain's development, has changed the organization of cerebral subsystems within the brain of schizophrenics.

Similar studies with autistic children found that one part of the cerebellum is smaller than normal in a large proportion of these subjects. The abnormality appears to result from inadequate development of the region rather than shrinkage, and it differs from abnormalities observed in several other disorders known to affect the cerebellum. In addition, the abnormal part of the cerebellum has been linked in animal studies to many of the behavioral functions affected in autism.

One of the most exciting outcomes of such studies will be a description of the pattern of affected and unaffected portions of the cerebellum. This finding could help us define the critical point in brain maturation when some agent such as toxicity, virus, or injury could disturb the growth of the affected structures.

Studies of children with Down's Syndrome confirm that cerebral abnormalities observed in autopsy studies are present early in the children's lives. MRI also shows subtle changes in brain structure accompanying conditions such as stroke, multiple sclerosis, old injury,

inflammation, or viral infection. Many of these changes are not discernible by any other means while the subjects are alive.

Neuroscientists are also finding brain structural abnormalities in older people who do not show symptoms of illness. In normal volunteers, these irregularities were rare in individuals under 50 years of age, but became more common as the subject's age increased. Further investigation found that the changes are associated in normal elderly with vascular risk factors, suggesting that they may reflect some latent defect in the brain's circulatory system. The significance of these signal abnormalities in individual cases is still uncertain, especially when they occur in association with other central nervous system abnormalities.

Aberrant signals indicating brain structural abnormalities have recently been detected in a large proportion of patients with manic depression. These patients averaged only 38 years of age, and healthy volunteers of the same age had no such brain abnormalities. This result was surprising, and its implications are not yet understood. The patients with the abnormalities were no older than the other patients, but seemed to have more severe illnesses, as reflected in a larger number of hospitalizations. Perhaps we have detected some precocious degenerative process manifesting as manic depression, or maybe the remnants of old injuries to the nervous system that prevent the normal function of certain brain systems. Future studies will undoubtedly solve this mystery.

Magnetic resonance spectroscopy: Finding the biochemical changes that accompany mental illness.

Researchers are now working to extend magnetic resonance technology into the area of measuring biochemical changes in the living brain; the resolution of magnetic resonance imaging is inherently superior to positron emission tomography. This variation, called magnetic resonance spectroscopy, measures the amount of specific chemicals present in different parts of the brain. For example, by looking at phosphorous-containing compounds, magnetic resonance spectroscopy can measure energy use throughout the brain. The level of one particular phosphorous-containing lipid increased in some regions of the brain when volunteers took lithium. This change may be related to the poorly understood therapeutic action of lithium in controlling manic-depressive illness.

Recently, scientists studying how benzodiazepines exert their effects used magnetic resonance imaging to construct a crude map of the receptors to which these drugs bind. The researchers attached a tiny magnetic complex to drug molecules and injected them into rabbits. The complex alters the magnetic field wherever the drug is, which distorts the signal received by the imaging device. The altered signals therefore indicate which parts of the brain contain receptors for the labeled drug. As this technique is improved, it should yield important information about biochemical changes in psychiatric disorders, such as possible alterations in receptor density. It should also provide new insights into how current drugs work to control mental illnesses and how these agents might be improved.

Future benefits.—Within the next few years, researchers will begin combining the images produced by neuromagnetic imaging and magnetic resonance imaging to provide both structural and functional information. Eventually, data from positron emission tomographic studies will be added. Researchers recently developed the first computer-based models of the head designed explicitly for coordinating neuromagnetic imaging data on functional signals with magnetic resonance images of anatomical structure. These dual-imaging computer models, now being tested, will provide a unified picture of the physiology and anatomy of human thought that will help guide further research into the causes of mental health disorders and their diagnoses.

Considering that these techniques are only a few years old, the advances seen already promise an exponential increase in our knowledge. Over the next decade, such studies should elucidate the brain circuitry involved in movement, communication, learning and memory, and attention. In addition, neuroscientists will be able to probe the so-called silent areas of the brain—regions whose functions remain unknown.

Neurophysiology.—Researchers have long been interested in defining brain function through electroencephalography (EEG) studies. Unfortunately, these techniques create far more information than can be comprehended by simple, unaided visual inspection. To solve this embarrassment of riches, investigators have devised computerized data extraction and analysis techniques to produce color-coded topographic maps illustrating key parameters derived from brain electrical activity. Statistical comparison of these images to those of normal, healthy patients can also generate maps of statistical differences between groups.

Although newer techniques have replaced EEG in most studies of brain function, computer-processed brain electrical activity mappings (BEAM), as the new EEG is called, will continue to add to our knowledge about brain processes in the years ahead.

Learning problems.—Individuals with dyslexia have been considered as having emotional problems or of simply not applying themselves to the task of learning to read. Since an emotionally disturbed child who does not read may be psychologically untestable, we may not know whether the child cannot read and is disturbed because he is fundamentally dyslexic or whether he cannot read because of severe emotional disturbance. EEG studies can help resolve the dilemma.

Brain electrical activity mapping indicates aberrant cortical function in dyslexia.

Brain electrical activity mapping recently provided convincing evidence that dyslexia is clearly associated with consistently aberrant electrical activity in two well-defined regions of the cerebral cortex, thus establishing the disability as inherently organic as opposed to inherently psychological. Moreover, the consistent nature of the electrical abnormality has led to current studies whose objective is to

provide criteria for the recognition of potentially dyslexic children prior to entering primary school to prevent school failure.

Physicians are well aware that prematurely born infants have an increased incidence of behavioral and cognitive dysfunction later in childhood. Recent studies of brain electrical activity in such children, tested at both infancy and school age, demonstrated consistent patterns. Aberrant activity is noticeable primarily in the frontal region and over the right hemisphere.

This activity correlates strongly with a behavioral pattern suggesting spatial problems, inappropriate social behavior, and motor systems malfunction. In contrast, language and reading function are only slightly disturbed, and brain electrical activity from the left hemisphere appears near normal. Thus, these children may suffer not so much from an inherent inability to learn to read and comprehend as they do from difficulties in social and behavioral adaptation which derive from frontal and right hemisphere systems.

Physical illnesses change the brain's activity, and could cause mental deterioration in the elderly.

Aging.— Recent studies of brain electrical activity during the processes of normal aging have shown some minor changes in brain electrical activity in healthy volunteers from age 30 to 80. In contrast, illnesses such as hypertension and diabetes produce clear changes in brain activity. Such changes were dismissed previously as signs of aging, but they may actually reflect the higher incidence of such medical conditions in the aged.

The message here is that if one is free of significant medical conditions, mental function may remain quite intact until very late in life. This emphasizes the need to recognize and treat these conditions, for they may play a significant role in the mental decline which is ordinarily attributed to the simple process of aging.

Depression.— Computer-analyzed brain activity measurement shows great promise in the ability to make important clinical distinctions between patients who appear demented but are really depressed and people who are showing initial signs of Alzheimer's dementia. Early in their course these differing clinical processes may appear nearly identical except through electroencephalographic studies.

Electrical mapping adds to understanding pathology of depression and schizophrenia.

Studies of depressed adults also suggest that more than one brain region may be involved in this disorder. In some patients, the right posterior hemisphere seems to be the most electrically aberrant; others show abnormal activity in the left posterior quadrant or in the left anterior quadrant. It may be, therefore, that factors clouding our ability to thoroughly understand depression stem in part from the fact that depression is a heterogeneous disorder, and that we might learn more by selectively investigating patients with one particular type of electrophysiological pattern.

Schizophrenia.— It has been widely known that in schizophrenics the

frontal lobes of the cortex show diminished metabolism and increased pathological brain wave slowing in the electroencephalogram. Recent electrical mapping studies, however, clearly demonstrated a second region of concern involving the left rear temporal region of the cortex. Such findings guide research in focusing on the brain systems of the temporal lobe, which may indeed be prominently involved in this complex and devastating clinical syndrome. Schizophrenia is believed by many to consist of not one but a number of diseases evidenced by a more or less common clinical picture. Electrophysiological studies show great promise in assisting clinicians in breaking schizophrenia into meaningful groups by objective criteria.

Future benefits.—In the practice of clinical neurophysiology, classic electroencephalographic evaluation will undoubtedly be replaced by quantified electroencephalogram and topographic mapping. The enhanced value of these techniques will place mapping systems in virtually every major hospital, since these techniques offer the possibility of more accurate and quantified diagnosis at a much lower cost than neuromagnetic imaging, positron emission tomography, or magnetic resonance imaging. It is not unreasonable to expect that it may be possible to predict a patient's clinical response to a therapeutic regimen. For example, it may become possible to determine which depressed patients will respond to lithium and which to more typical mood elevators.

Unquestionably the most intriguing study would be to refine our understanding of normal thought processes. This would be accomplished by the placement of hundreds of recording electrodes on the scalp and the development of ever more sophisticated techniques for detecting patterns of activity in response to alteration of brain function. It is conceivable that intelligence and behavioral style may become definable or recognizable by characteristic patterns of brain activity. Subjects at risk for alcoholism, schizophrenia, or depression may be identifiable well before onset of clinical symptoms. Youngsters at risk for dyslexia may be identified and the trauma of basic learning skills failure in the early grades avoided. Patients with neurological lesions at risk for change may be followed over time. Adverse change in brain function may be detected in advance of clinical deterioration, thereby permitting timely therapeutic or preventive strategies.

Treating Major Mental Illness

Understanding Current Therapies

In 1954, psychiatrists first successfully treated psychotic patients with chlorpromazine and, in so doing, demonstrated that psychoses in general, and schizophrenia in particular, might have specific, identifiable central nervous system underpinnings. Today, drugs used to treat psychiatric disorders play a crucial role in uncovering the biological bases of these diseases. Elucidating how and where these compounds act in the brain should give us important clues about not

Psychotherapeutic drug helps elucidate disease mechanisms.

only the normal functioning of the brain, but the biological basis of the abnormalities themselves.

Antipsychotic agents.—Much of the research on drug effects has been done with antipsychotic agents, also called neuroleptics, used to treat schizophrenia. Cumulative evidence from basic studies has clearly shown that at least one of the major actions of antipsychotic drugs is to block dopamine receptors in the central nervous system. These findings led neuroscientists to propose the well-known "dopamine hypothesis" of schizophrenia. However, drug therapy ameliorates some symptoms but does not produce a cure, and many early antipsychotics also had numerous side effects, such as the nervous system disorder known as tardive dyskinesia. Thus, the dopamine hypothesis cannot be the full story in schizophrenia.

Further research with different classes of antipsychotic agents revealed at least two types of dopamine-utilizing nerve cells where these drugs act. One type is responsible for tardive dyskinesia effects, while the other seems to play a role in the disease's symptoms. As a result, pharmaceutical chemists are now creating antipsychotic agents which act only at the dopamine nerve sites which are primary in schizophrenia.

Researchers were mystified by the finding that antipsychotic drugs can block dopamine receptors after a single dose of the drug, but that the therapeutic actions can take weeks, sometimes months, to develop. Neuroscientists therefore turned to examining the actions of repeated exposure to these drugs on dopamine cell activity. They found that these drugs inactivate dopamine-containing neurons in a time-dependent fashion. Other studies showed that the amount of dopamine released by the neurons decreases as well.

Molecular neurobiology of dopamine system leads to better drugs for treating schizophrenia.

Investigators working on this problem predict that further study using the tools of molecular biology will finally solve the mysteries surrounding the action of antipsychotic agents at dopamine neurons. It may be, for instance, that the various subtypes of dopamine receptors known to exist react differently to antipsychotic drugs. Isolating the genes for those receptors will enable scientists to produce them in large amounts, making further study on the drug-receptor relationship possible.

Affective disorder treatments.—Antidepressants appear to alter the activity of neurons that use the neurotransmitters norepinephrine and serotonin (monoamines), leading to the hypothesis that depression is caused by altered activity of those neurons. That theory is supported by studies showing that drugs that change norepinephrine and serotonin levels in the brain also produce depression.

Most antidepressants belong to one of two major families: monoamine oxidase (MAO) inhibitors and tricyclic antidepressants. Experiments in animals and humans have shown that MAO inhibitors appear to increase the amount of monoamine neurotransmitters by blocking the

action of the enzyme MAO, which breaks them down. Some tricyclic antidepressants seem to make more monoamine neurotransmitters available in the synapse by slowing its reabsorption by nerve cells.

Currently, some studies show that antidepressants increase the sensitivity of monoamine-using nerve cells, while other experiments yield opposite results. Researchers are certain that the final answer will be discovered soon, and that it will provide clues to help them design better drugs for treating depression.

Lithium, a major therapeutic agent in affective disorder, exerts both prophylactic and acute therapeutic action in mania and in some forms of depression. Studies of lithium's mechanism of action have focused on the effects on biogenic amine neurotransmitters that are involved in actions of antidepressant drugs and may play a role in the pathophysiology of affective disorder. The ability of lithium to affect the phosphoinositide (PI) system, which is stimulated by biogenic amine neurotransmitters, has recently led to suggestions that interference with the PI cycle may mediate lithium's therapeutic action.

The PI cycle is a major second messenger system mediating actions of numerous hormones and neurotransmitters. Receptor stimulation triggers the cleavage of phosphatidylinositol-bis-phosphate, giving rise to diacylglycerol and inositol trisphosphate. Inositol trisphosphate mobilizes intracellular calcium, while diacylglycerol activates protein kinase C by enhancing its affinity for calcium, which stimulates protein kinase C activity. Phosphatase enzymes sequentially remove phosphate groups from inositol trisphosphate, giving rise to free inositol that is then reconverted to phosphatidylinositol-bis-phosphate, reinitiating the PI cycle.

Inhibition by lithium of phosphatase activity causes a buildup of various inositol phosphates. In principle, this action could slow down the PI cycle, dampening cellular responses to neurotransmitters. However, the relevance of this effect of lithium to its therapeutic action is unclear. Further evidence is required to show that lithium's effect on the PI cycle actually alters the cellular response to neurotransmitters.

Light therapy.—Another form of treatment—exposure to bright light—for certain types of depression has gained popularity in the past few years. The study of the biology of light and circadian rhythms has proven to be a particularly rich source of information.

Bright lights prove valuable treatment for seasonal depression and other mood disorders.

Early in the 1980s, researchers recognized a special type of depression, seasonal affective disorder. These patients experience the onset of depressed mood in October or November as the days grow short. During the winter, they are sad, fatigued, and may suffer such low energy that they are occupationally disabled. Sometimes they need hospitalization. As the days grow longer in March and April, seasonal affective disorder patients may suddenly turn quite cheerful as their energy and enthusiasm return.

Scientists tried to help these patients by artificially extending day length with very bright light. Within a few days, most seasonal affective disorder patients exposed to such light display dramatic improvements in mood. Some patients find that an hour or two of bright light exposure a day is sufficient to eliminate their winter symptoms. Within a few years and at remarkably low expense, this new and natural treatment has become common medical practice. Nevertheless, extremely important research questions remain to be examined.

First, physicians are uncertain about the most favorable time of day for treating seasonal affective disorder patients with light, a matter of obvious practical importance. Some researchers believe the early morning hours just after arising to be best, but others get good results with evening or even midday light. Further testing of treatment timings is clearly needed to enable these patients to gain the most benefit with a minimal time spent sitting in front of special bright lights. The optimal color and intensity of light treatment also need further examination.

Preliminary studies of bright light treatment for depression in general also show significant benefits, although not as dramatic as in seasonal affective disorder patients. Light treatments may indeed compare favorably with the short-term benefits of antidepressant drugs, and may hasten the effect of the drugs. Further testing of the longer term benefits of light treatment are urgently needed to determine whether it will provide a useful alternative to current therapies.

Americans receive remarkably little daily exposure to outdoor light, even in good weather. As people moved from farms to cities, they also moved indoors. If the human organism was designed to be outdoors most of the time, then our bodies may be interpreting normal indoor lighting as a life of almost perpetual darkness. Much more needs to be learned about light exposure and its relationship to depression and other medical illnesses. Lighting up America may be a way to enhance its vigor and productivity.

Antianxiety drugs.—Gamma aminobutyric acid (GABA) is the main inhibitory transmitter in the brain. The two families of GABA receptors, $GABA_A$ and $GABA_B$, possess different pharmacological profiles and use different transduction mechanisms. Thus, GABAergic transmission is accomplished by a number of routes, some involving the activation of ion channels, others involving the initiation of intraneuronal metabolic events.

New concept of synaptic transmission provides insight into mechanism of antianxiety drug action.

In addition to multiple transduction mechanisms, the GABA receptors include multiple regulatory sites through which GABA exerts its action. The $GABA_A$ receptor is composed of two dimers, each containing an alpha and beta subunit. The recognition site for the primary transmitter, GABA, is always located on the beta subunit. However, a number of other binding sites, which have high affinity for specific drugs, exist elsewhere on the receptor protein. These findings provided

the experimental underpinnings for a new concept of synaptic transmission: polytypic signaling at single synapses.

We now know that the benzodiazepines exert their anticonvulsant and anxiolytic effects not by acting on their own, but by increasing the probability that the primary transmitter will act on the $GABA_A$ receptor, i.e., that the influx of chloride ions into the postsynaptic cell will be increased by a given amount of GABA. Furthermore, the same modulatory site on the $GABA_A$ receptor that binds the benzodiazepines can also bind another group of drugs, the betacarbolines. These drugs, which are proconvulsant and anxiogenic, decrease the effectiveness of GABA.

The matching of behavioral effects to receptor regulation by signals other than the primary transmitter may seem logical and elegant now, but when first proposed, it met considerable resistance from neuroscientists. The tenets of monotypic signaling and the supremacy of the neurotransmitter were so firmly held that any suggestion of signal modulation by other substances coexisting with the transmitter in the axon terminal and acting at the same synapse seemed unreasonable. However, the weight of experimental evidence won out, and the concept of modulation of primary transmitters is gradually replacing the monotypic signaling model.

An endogenous anxiogenic.

The modulatory effects of benzodiazepines and beta-carbolines on GABAergic transmission were of obvious pharmacological significance, but further research was required to explain it physiologically. The search for an endogenous substance that acts on the $GABA_A$ receptor led to its discovery in 1978. Diazepam-binding inhibitor (DBI), a neuropeptide, was found in the brains of several mammalian species, including humans, capable of displacing both benzodiazepines and beta-carbolines from their binding sites on $GABA_A$ receptors.

Since that time, evidence from molecular biological, electrophysiological, and immunochemical studies has revealed that DBI is the probable precursor for a family of modulators of the $GABA_A$ receptor. Three such modulators in this family have been detected in rat brain and their amino acid sequence determined. These modulators, which appear to be coreleased from nerve terminals with the primary transmitter GABA, act physiologically like the anxiogenic beta-carbolines, decreasing the likelihood that GABA will open the receptor-coupled chloride channels.

Studies are proceeding on the other modulatory sites of the GABA receptor system. However, it is already clear from the work on the GABA/benzodiazepine/chloride receptor complex that regulation of receptor function is achieved through polytypic signaling and not through simple on-off control exclusively mediated by the primary transmitter. Hence, we now have both an intellectual construct and experimental support for a new focus in neuropharmacology—away from the concept of transmitter agonists and antagonists and toward the development of drugs that mimic endogenous modulators.

Developing New Therapies

Finding better ways to treat mental health problems is a top priority of neuroscience research. No medication currently in use is truly effective in treating all the symptoms of the disorders for which they are prescribed, nor are they always equally effective in males and females. Many avenues are being explored, some of which show tremendous promise for advances in the near future.

Computer-aided molecular modeling facilitates rational drug design.

Computer-assisted molecular modeling.—Major advances in computer hardware and software will allow researchers to use computer-assisted molecular modeling to more efficiently design new drugs to intervene in the many disease states that adversely affect our lives, as well as to uncover many aspects of nerve function. The ultimate promise of model building is to gain insight into how receptors and enzymes interact with smaller molecules, thereby providing an in-depth understanding of the molecular basis for drug specificity.

The relationship between a molecule's three-dimensional structure and its biological activity has long fascinated scientists. For example, a linear polymer of amino acids is simply a protein; but if the protein is coiled into a three-dimensional shape, it becomes an enzyme. This enzyme now has active sites where chemical transformations can occur. Similar cases, in which the overall shape of molecules both large and small determine biological activity, exist throughout biochemistry.

In the not too distant past, chemists tried to discover the true chemical forces behind these relationships by studying analogs containing a range of different atoms and substituents. But this was labor-intensive and time-consuming, and subject to human bias. Misleading, if not incorrect, conclusions could arise from the implicit assumption that the altered atom/group is the only site affected, when, in fact, a change in one part of a molecule may alter the secondary structure in another part.

The development of today's reliable computational procedures promises to overcome inherent bias, quantify structural and electronic interaction, and provide deeper insight into molecular phenomena that may have gone unrecognized. Incredible advances in computers permit the scientist to simply sketch a molecule of interest, such as dopamine or acetylcholine, onto an electronic pad or directly onto a terminal with the aid of a light pen. The structure then appears on the screen, with the various fragments displayed in an array of colors for better viewing. Many programs already have a library of structural fragments such as nucleotide and amino acid building blocks. Atomic substitutions and insertions can be rapidly achieved with various graphic menus.

Once the desired structure has been defined, it can be analyzed by any number of computational procedures that theoretical chemists have

developed over the past two decades. When the calculations are completed, the optimal three-dimensional structure is displayed on the screen. Researchers can then check critical bond lengths, angles, and distances between various important fragments. Most of the currently available programs allow the researcher to overlay one molecule on top of another. Thus, the three-dimensional structures of several molecules, with different biological activities, can be compared. In this manner, researchers can pinpoint those structural details that are important to biological activity and those that are not.

Three-dimensional visualization of brain molecules.

The development and refinement of molecular dynamics programs will enable scientists to see biochemical events on the computer screen. Researchers will then be able to witness an enzyme catalyzing a substrate's conversion to product, or a neurotransmitter binding to its receptor protein, and thereby come to better understand the conformational changes that occur during these processes. Investigators may even directly interact with a hypothetical enzyme or a receptor: instead of viewing the three-dimensional protein on a two-dimensional computer screen and giving commands from a terminal to affect that protein, the scientist will wear special helmets and gloves that emulate being inside that protein—visually, tactilely, and verbally. Such technology already exists on a limited basis for .NASA; future prospects are astounding.

During the next decade, modeling of important molecules in the central nervous system—receptors, enzymes, structural proteins, neurotransmitters and drugs—will become routine. Advances in computer hardware and software, protein purification techniques, immunology, and molecular biology will all enable researchers to design selective and site-specific drugs in a rational and efficient manner. Few of today's pharmacological agents are the product of rigorous computer-assisted drug design. Certainly, no drugs that work in the brain have been produced via these means to date. The next decade will see the realization of such events, and their impact on science and medicine will be apparent for many more decades to come.

Brain transplant techniques.—A novel approach to treating disorders originating in the brain is to replace damaged brain tissue with healthy tissue. Neuroscientists hope to one day perform brain tissue transplants in much the same way that physicians now perform kidney transplants.

Replacing damaged brain tissue.

Scientists have already succeeded in transplanting dopamine neurons from the midbrain of rat and primate fetuses into the brains of adult rats and primates at a site just over the target area for those neurons, a region called the corpus striatum. The adult animals had been previously treated with a neurotoxin that specifically destroys dopamine neurons, producing a characteristic movement disorder. Within weeks after the dopamine-containing neurons were transplanted, the movement disorder was greatly reduced. Animals treated with the neurotoxin did not improve without the neuronal transplants.

Examining the animals' brains showed that the transplanted embryonic neurons sent dopamine nerve fibers into the corpus striatum, where they formed nerve terminal networks. The amount of growth of the dopamine-containing fibers correlated well with the decrease in abnormal behavior. Other more complex types of behavior also became more normal as a result of the neuronal graft.Subsequent investigation has shown that the particular kind of behavioral deficit that is relieved by the transplant depends upon where the graft connects to the corpus striatum. These experiments suggest that the dopaminergic innervation to the corpus striatum is topographically organized with respect to specific kinds of behavior.

Parkinson's disease is caused by a similar deficit of dopamine-containing neurons in the brain. Because human fetal material is virtually impossible to obtain, investigators had to look elsewhere for transplant materials that could repair the behavioral deficits associated with loss of dopaminergic neurons. The adrenal medulla, which sit on the kidneys, were logical candidates because their cells synthesize compounds that can serve as precursors to dopamine. In animal experiments, adult adrenal medullary cells transplanted into damaged animal brains produced about a 50-percent improvement in movement disorders. Microscopic examination showed that the adrenal medullary cells had developed a characteristic appearance and grouped themselves into small clusters within the graft.

Most recently, in both Sweden and Mexico, transplanting cells from the adrenal medulla into the brains of young Parkinson's patients resulted in detectable clinical improvement. This represents, in part, a culmination of the basic investigations into the viability of embryonic dopamine neurons and adrenal medullary cells and their ability to reverse behavioral abnormalities associated with loss of dopamine-containing neurons in the adult animal. The results of such experiments clearly challenge previously held notions about the irreversibility of certain types of brain damage.

Adrenal transplants: Clinically successful, but why?

Since the report of this neurosurgical approach in humans, animals rendered Parkinsonian by drugs have been given adrenal medulla implants, leading to remarkable improvement. However, contrary to transplants of fetal brain tissue, the adrenal medullary cells implanted into the caudate nucleus do not grow new neurons or reinnervate the dopamine-depleted caudate nucleus of the experimental animals. Instead, the brains of these animals are reinnervated with nerve processes that originate from surviving dopamine neurons present in their midbrain. This fact leads to the exciting possibility that a substance in the adrenal medulla can induce existing axons to grow and reinnervate the caudate nucleus. Perhaps more importantly, this substance may save dopamine-containing neurons otherwise destined to die.

An alternative to transplanting tissue from another part of the body is

Growing replacement brain cells in culture.

to use matched nerve cells grown in tissue culture, something akin to a tissue or blood bank. Over the past few years, neuroscientists have made great strides in growing brain tissue outside of the brain and inducing that tissue to grow when inserted into the brain of another animal.

In the simplest kind of tissue culture, a small piece of tissue is excised from the organism and placed in a glass dish containing a fluid medium similar to blood plasma. Oxygen is supplied, and the tissue must be sufficiently thin to allow the oxygen to diffuse throughout it.

A second type of tissue culture breaks down the tissue into individual cells and grows them as a suspension in a fluid medium with added oxygen. Within a few days the neurons begin to extend cellular processes, called neurites, that are precursors of mature dendrites and axons. Such cultures survive for weeks and are referred to as "monolayer" cultures since the cells grow in two dimensions and the culture is only one cell deep.

Another way of culturing dissociated single cells is to allow them to aggregate in rotatory tissue culture. For example, embryonic midbrain-containing dopamine neurons, as well as other neuronal types, can be removed from experimental mice and dissociated into a single-cell suspension. Less than 1 percent of these dissociated cells are dopaminergic neurons. When placed in a rotating flask filled with culture media, the cells collide with and stick to one another, forming hundreds of spherical clumps less than 0.3 millimeters in diameter. These cells can be cultured alone or combined with dissociated cells from other areas of the brain. Thus, dopamine-containing neurons of the midbrain can be cultured in the presence of their midbrain neighbors, or with cells from distant regions in the brain. These small aggregates represent, in a sense, tiny "minibrains." Such aggregates have the advantage when compared to monolayer cultures that the neurons are free to develop in three dimensions as they do in the intact brain.

Target neurons are needed for proper neuronal cell growth.

Over a 3-week period in aggregate culture, dopamine-containing neurons develop in a manner indistinguishable from normal development in the intact brain provided that cells with which they normally make connections are present within the cultures. If the target cells are absent from the cultures and replaced by nontarget cells, the dopamine neurons fail to elaborate axonal processes nor do they survive as well as they do in cultures with target cells. This is an example of a target cell-dependent program of neuronal development.

Studies with cholinergic neurons—those that use acetylcholine as a neurotransmitter—have yielded similar results: cholinergic neurons do not develop properly nor survive well in the absence of the cells to which they would normally send their axons and make synaptic connections. These and other studies have led investigators to speculate that Parkinson's disease and Alzheimer's disease may result from a deficit in

the ability of target cells to provide special growth-sustaining, or trophic, substances necessary for the continued maintenance of dopaminergic and cholinergic nerve cells, respectively.

In the coming years, neuroscientists will refine their techniques for growing neurons in culture and will perfect their methods for getting these cells to grow normally when reinserted into a living brain. The existence of cell banks containing cell lines, each of which produces a characteristic neurotransmitter substance, could, in theory, allow one to specifically replace particular subsets of neurons that had been lost to disease processes. Hence, either use of trophic factors or the transplantation of cells that produce the particular neurotransmitter that is missing because of neuronal death, or these two procedures in combination offer the hope of conquering some of mankind's most devastating mental and neurological disorders.

Genetic repair of mental illnesses.

Genetic therapies.— Scientists predict that by the year 2000 virtually all mutant genes responsible for brain disorders in humans, including those responsible for manic-depressive illnesses and schizophrenia, will be mapped onto the human genome. These mutant genes will be isolated and cloned, and their gene products identified. In the future, it may be possible to cure some heritable diseases by replacing a missing gene product, an enzyme, for example, or by blocking the expression of the mutant gene product. Genetic defects may eventually be corrected through insertion of normal genes in place of defective ones.

With further molecular neurobiological experimentation, the control of the brain's molecular mechanisms will become well understood. Why, for example, are certain genes expressed in only one tissue and not in another? How are they expressed at the appropriate time in the appropriate tissue? The genes that direct developmental events and the processes that control them are just starting to be revealed. The intensive research needed in this field will rely heavily on the use of animal mutants with abnormal behaviors.

Animal experiments indicate that environment and heredity are intertwined. Many diseases may require more than one "favorable" circumstance in order to be expressed, i.e., both a genetic susceptibility and an environmental condition. Where gene or gene product replacement therapy is not possible, knowledge of the chain of events leading to mental illness may enable clinicians to develop intervention strategies.

Modeling Human Illnesses in Other Species

Animal models open up new vistas in mental health research.

Animal models of human disorders are extremely useful, particularly because they permit detailed study of physiological processes. Considerable effort has been devoted to developing animal models of psychopathology.

Assay models use an animal's behavioral or physiological responses to

assess physiological processes that evidence suggests are important in a disorder. For example, drug studies indicate that altered dopamine function is important in schizophrenia and Parkinson's disease. Rats show turning (rotational) behavior when receptors for dopamine in the brain are stimulated. The sensitivity of receptors and the activity of the dopaminergic system in the brain can be assessed in rats by measuring their turning behavior. Thus, this response in the animal serves as an assay for a physiological function of importance in behavioral pathology.

Assay models are used primarily for screening and developing new drugs. By permitting investigators to determine how various compounds affect the physiological processes important in pathology, these models make it possible to assess rapidly a drug's potential usefulness and, in some cases, to discover new drugs that unexpectedly affect an important physiological process.

Homologous models endeavor to recreate symptoms of the human disorder in another species. Once perfected, these models can be extremely valuable. Since a perfected homologous model reproduces many symptoms of the disorder without making any assumptions about physiology, researchers can test any type of potential treatment on the animal model to see if it can reverse the prevalant symptoms. The model can also be studied to discover the underlying causes of the symptoms.

Homologous models for a number of mental illnesses are currently being developed. This will facilitate the discovery of the underlying physiological defects in the disorders that the models represent. Given the ability to dissect and measure neurochemical and anatomical systems in animals, major advances are certain to occur following the development of adequate models.

Animal model of depression mimics symptomology of depressed humans: decreased appetite, weight loss, malaise, and sleeplessness.

Some of the greatest strides have been made in modeling depression. From crude pharmacological manipulations that produce immobility in treated animals, scientists have now reached the point where animal models of depression approximate, and may actually meet, criteria for diagnosis of human depression as set forth in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-III). Different animal models have even been developed for different subtypes of depression.

The best depression model now available is based on stress-induced depression. When animals are exposed to stressful conditions over which they have no control, they show numerous symptoms seen in human depression, including decreased food and water intake, loss of body weight, loss of normal competitiveness, decreases in aggressiveness and sexual behavior, and loss of sleep marked especially by early-morning awakening. Similar symptoms are found in human patients who become depressed after being exposed to stressful conditions, and particularly after experiencing stressful conditions that they felt they could not control. The model also resembles human

depression with respect to treatment response, because it can be alleviated by a variety of antidepressants.

Depression model allows study of biology of depression.

With this model, researchers can study the underlying pathophysiology in depression. Neuroscientists have known for more than two decades that the neurotransmitter systems that utilize biogenic amines are probably involved in depression, and many of the drugs that ameliorate depression affect these amines. However, the disturbance of amines in the brain of depressed patients is not universal; different patients respond to certain drugs and not to others, clearly demonstrating that limited and specific components of the systems are involved in depression, and not all depressions are the same.

Receptors may be the key in treating depression.

Researchers will soon be able to study different branches of the amine systems in human subjects, as new techniques allow safe, minute observation of these areas of the brain. Currently, investigators using animal models have found that depression occurs when norepinephrine neural transmission decreases in the brain region where norepinepherine cells are most heavily concentrated (the locus coeruleus) and, as a consequence, norepinepherine transmission then increases in brain regions to which axons of locus coeruleus cells project. This picture of depression is more complicated than "norepinephrine is decreased" or "norepinephrine is increased," and it may well explain why many drug treatments have side effects and are less successful than expected. Nevertheless, it would seem that this complexity can be dealt with by drugs targeted at specific receptor types.

Researchers have also identified specific brain regions and neurochemical responses that result in particular aspects of the depression syndrome. For example, neuroscientists have distinguished the brain regions that produce inactivity or lethargy from those tied to an inability to concentrate, both symptoms of depression.

Brain's reward system may play role in mental illness.

Depressed animals fail to enjoy rewarding stimuli, a highly important characteristic in both depression and schizophrenia. Investigators are increasingly turning their attention to reward systems in the brain, first revealed by electrical brain stimulation experiments. Though research in this field has been ongoing for more than 20 years, only recently has the evidence made clear that the phenomenon of electrical brain stimulation may indeed tap into the brain pathways for reward mechanisms, rather than the reward features of these experiments being some artifact of the procedure. Investigators working with animal models of depression have indeed found that behavior motivated by rewarding brain stimulation is markedly reduced in these models. This is but one example of how determining the basic neurophysiology of particular responses will allow the dissection of large psychiatric syndromes into their basic components, enabling us to better treat and perhaps prevent these disabilities. Eventually, treatment of patients may be directed at their particular array of symptoms rather than at a vague disorder in general.

The development of one animal model recently led directly to improved clinical treatment for humans. Researchers sought to construct an animal model of early maternal deprivation. In this type of homologous model, instead of reproducing a particular disorder or syndrome based on the behavior of the animal, an environmental manipulation is applied that represents what occurs in the human situation. The investigators intended to study in the animals the physiological effects of maternal deprivation.

Depression model shows maternal contact is key to better growth in premature infants.

While constructing the model, the researchers discovered that many metabolic changes occurred as a consequence of taking young rat pups away from their mothers, and these changes persisted even if the pups were nourished adequately. The loss of interaction with the mother was the critical factor. Growth and growth-related processes essentially stopped when the animals were removed from their mothers, reminiscent of the retarded growth seen in humans deprived of nurturing maternal contact at an early age.

Researchers found that the intense stroking behavior that the mother rat administered to the pups was important in keeping active the significant biochemical responses involved in the growth process. This suggested the possibility of applying tactile stimulation to speed up the growth processes of premature human newborns who must be separated from their mothers. A major program was initiated to provide tactile stimulation to premature infants, and these results now show significant increases in the rate of growth, with greater weight gain and more alertness. The cost saving is also appreciable; the average hospital stay for stimulated newborns is 6 days shorter than that of newborns not subjected to this kind of stimulation, resulting in a saving of $3000 per infant. This is but one example of how a homologous model has led directly to an innovative clinical treatment applied to humans.

Models for schizophrenia badly needed.

Perhaps the greatest need is for models of the psychotic disorders. Schizophrenia has been difficult to approach in animals because the most salient deficit of the human disorder is disturbed thought, which is assessed through verbalization. As a consequence, the vital and pervasive problem of schizophrenia has proved quite difficult to approach by an animal model. Such models as do exist have been based mainly on drug administration (such as amphetamine) that gives rise to behavior in the human that very much models psychotic behavior. However, these pharmacological models are the weakest in the homologous category.

Considerable advances in this area will come from studies of learning and from the approximations of thought processes in animals. As investigators examine higher mental processes in animals, and begin to approximate what might be called cognitive processes in animals, the opportunity to construct animal models of disturbed thought processes increases greatly.

One highly important development anticipated in the near future is the

Genetics offers a new approach to model psychiatric disorders.

appreciation of genetic determinants in animal models. To date, most animal models have been constructed on the theory that any member of a particular species can be made to show the appropriate abnormal behavior given the right treatment, whether the treatment be pharmacological or environmental. While this assumption might seem valid when pharmacological or neurological manipulations are used, scientists are beginning to question its validity for environmental manipulations, which are most likely to yield adequate homologous models.

Investigators are already beginning to pay much more attention to the fact that certain individuals are likely to develop a given disorder while other individuals of the species are unlikely to develop the disorder, and perhaps never would develop the disorder, regardless of the treatment. The evidence showing the heritability of the major mental illnesses will lead researchers to increasingly focus on developing genetic lines of animals that are susceptible to the disorders they wish to study. Just as no two humans are equally likely to become depressed given the same change in their environment, animals differ in the likelihood that they will become depressed. The appreciation that animals can be bred for susceptibility to particular disorders and that adequate models of depression and psychosis demand that particular lines be specifically bred for their susceptibility to these disorders will be a major step toward the development of truly homologous models.

Mind Over Illness

Anyone who has ever blushed in embarrassment knows that transient feelings can superficially involve the body as well as the mind. Centuries of medical experience testify that psychological factors can also have more serious correlates in human physiology. In some persons, strong emotions can actually kill by triggering cardiac death. In others, the effects of stressful situations are more insidious, predisposing to a variety of psychiatric and physical disorders. For example, separated and divorced individuals are at greater risk than married or single adults for both mental and physical illness, with higher death rates from infectious diseases, including six times as many deaths from pneumonia, and with a significantly higher incidence of cancer.

The other side of the coin is that positive emotions can also affect health. Optimistic, committed persons seem to gain some protection from their hardy personalities against the power of stressful life events to predispose to illness. For instance, AIDS patients who feel in control of their lives tend to live longer than do those who feel helpless.

Emotion-health link grows stronger.

Mental effects on physical health are mediated by the nervous system, which regulates both the mind and the body. In recent years, investigators have begun to study the mechanisms by which the nervous system translates psychological factors into physiological states that can affect physical health. In particular, a growing group of

scientists are working to understand how the brain influences, and is influenced by, the various systems that defend and repair the body's tissues.

One of the body's most important defense systems, the immune system, protects against infectious diseases and cancers. The immune system has built-in controls that normally keep it properly responsive to dangerous entities. However, it can become under- or over-responsive. When it underreacts to microbes and tumor cells, infections and cancers occur; when it overreacts to harmless substances or the body's own tissues, allergies and autoimmune diseases such as rheumatoid arthritis occur. Defects in immune regulation can be fatal, whereas optimal immune responsiveness protects and restores health.

Evidence is increasing that an individual's evaluations of life experiences can affect the responsiveness of their immune systems through biochemical changes in the nervous system. The excitement being generated in this field, psychoneuroimmunology, is attracting scientists from many areas of expertise, and this interaction among different specialties should quickly upgrade our understanding of the immune response. By unraveling the complicated relationships between mind, brain, and disease resistance, neuroimmune physiology offers great promise for the development of new and cost-effective preventive and restorative drug therapies, psychotherapies, and self-therapies against infections, cancers, allergies, and autoimmune disorders.

Data from both animal and human studies clearly show that a variety of stressors can impact on the immune response. Does the equation go both ways? Can an intervention that reduces stress enhance the immune response, or at least return it to a normal baseline?

Positive mental attitude translates into better immune function.

By measuring various indicators of immune competence, researchers recently reported that immune function improved noticeably in individuals trained in progressive relaxation. Now the question becomes: Does improved immune function translate into better overall health? While it is reasonable to assume that both short- and long-term decreases in immunity may have deleterious consequences for health, and vice versa, researchers have yet to start the longitudinal studies that will explore the magnitude of the relationship and its association with the incidence, duration, and intensity of infectious disease and cancer.

Prospective studies with at-risk groups like the elderly or workers in high-stress jobs will provide a clearer picture of the impact on health. Poorer immune function has already been associated with higher rates of mortality in individuals over 80 years of age. Pneumonia and influenza constitute the fourth leading cause of death among the elderly. But the death rate from pneumonia for elderly psychiatric patients is 50 times higher in the first year after hospitalization than among their age-matched counterparts in the general population. The

ratio drops to 20 times higher by the second year of hospitalization, suggesting that the hospital environment per se may not be as important a factor as the transition.

With these issues in mind, it may be possible to devise various psychological therapies to improve physical health. If researchers can demonstrate that psychological intervention, such as the use of progressive relaxation, can modulate the immune response in a positive direction, simple preventive techniques might be developed to reduce the incidence of severe illness in specific high-risk populations.

A two-way street: A sick body can cause a sick mind.

The mind-body connection is not a one-way street. Many physical illnesses can cause depression and other psychopathological states. For example, systemic lupus erythematosus can cause a transient psychosis, believed to be mediated by antibodies. Depression is one of the initial and sustained symptoms of pancreatic and other cancers. These illnesses involve the immune system. Therefore, immune failures may contribute to mental illness, and immune success may protect against mental illness.

Research in this area is only beginning, but recent studies have already shown that the major organ of the immune system, the thymus gland, sends out neurons that connect to the brain. Why this connection should exist is a mystery, but the answer to it could provide vital information for those trying to develop new therapies for mental illness.

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PROSPECTS IN BASIC NEUROSCIENCE:
A Quantum Leap in Understanding the Brain

In the neurosciences, perhaps more than any other field of medical research, clinical advances derive primarily from basic research. Studies at the cellular and molecular levels of the adult brain, with its trillions of connections among its billions of neurons, are furthering our understanding of the central nervous system and how it controls behavior. The pace at which neuroscience research is progressing today promises a bright future for the treatment of mental disorders.

Forming the Nervous System

Proper development of the brain is critical to later mental health and behavioral stability. Disorders of brain development can only be understood by studying the multiple, complex factors that contribute to the formation of appropriate connections between neurons of given neurochemical types.

Brain development is critical to mental health.

The template for making the brain, like that for the rest of the body, is encoded in genetic material. Discovering how genes direct the brain's development represents one of the great challenges to contemporary biology. The brain contains billions of nerve cells arranged in a specific and intricate way. These neurons are also specific in the connections they make with other neurons, often at a considerable distance. For example, a neuron in the brain may connect with another neuron at the base of the spinal cord.

Genetic abnormalities may lead to behavioral disturbances through alterations in the way neurons migrate to and establish specific connections with other neurons. Just as some brain connections in birds are different from those in mammals, leading to a range of differences in behavior, so, too, on a more subtle level, some neuronal connections in people predisposed to manic-depressive psychosis or schizophrenia may prove to be significantly different from those in normal people.

Some exciting advances in this field are coming from studies of the nervous systems of lower invertebrates. For example, researchers are identifying genes that regulate the development of specific subsets of neurons. In these studies, investigators use monoclonal antibodies to identify specific neuronal populations and to detect molecules on the surface of neurons that are critical for migration and recognition during development of the nervous system. Finding these genes and surface molecules provides tools for the next step in unraveling the complex process of proper neuronal migration and connectivity.

Discovering molecules that hold nerve cells to one another.

In higher organisms, great advances have also been made in studying surface molecules and glial cells that play a role in neuronal migration and formation of neuronal connections. Recent studies have shown that molecules such as laminin are critical for neuronal growth. Other investigations have identified cell surface molecules such as N-CAM, and work is now underway to characterize the role these surface molecules play in neuronal interactions.

Developing nerve cells have definite targets.

Another way of studying brain development is to see what happens when separated nerve cells are placed in a Petri dish and allowed to grow. When researchers did this experiment with dopamine-containing neurons, the cells' development over a 3-week period was similar to that which occurs in the intact brain. This normal-looking growth only took place, however, when cells of the corpus striatum or frontal cortex were also present in the cultures. These are the target cells with which dopaminergic cells form synapses in the brain. If the target cells were absent from the cultures and replaced by nontarget cells, the dopaminergic neurons failed to send out axons and, in fact, did not survive as well as when target cells were present. Studies with cholinergic neurons have yielded similar results, that is, cholinergic neurons do not grow properly, nor survive as well, in the absence of the cells to which they would normally send their axons and make synaptic connections. These and other studies have led investigators to speculate that Parkinson's disease and Alzheimer's disease may result from a deficit in the ability of target cells to provide the growth-promoting, or trophic, substances that are necessary for the continued maintenance of the dopaminergic and cholinergic nerve cells, respectively.

Alzheimer's and Parkinson's diseases may be due to lack of trophic factors.

Another feature of the in vitro development of these neurons is the clustering of the dopaminergic and cholinergic neurons within individual aggregates, much as neurons in the developing brain form nuclei. Neurons originally distributed randomly in the starting cell suspension retain the ability to migrate within the culture, recognize other cells, and form neuronal groupings. This property of homotypic recognition has been observed for every neuronal type that researchers have studied, including the target cells of the dopaminergic neurons in the corpus striatum and the target cells of the cholinergic neurons in the area of the brain known as the hippocampus.

Understanding brain development through changing the genetic code.

Within the next few years, molecular biologists will perfect the techniques for introducing new genes into mammalian cells, homologous recombination. With techniques that promote homologous recombination in mammalian cells, neuroscientists will be able to determine the role of specific genes and their products. Researchers will also use homologous recombination of mutated genes to examine their function in complex developmental processes using transgenic mice. The transgenic mouse, now being developed, is very important for such analysis. Foreign DNA is incorporated into the genes of a fertilized mouse egg that is then implanted in a mouse womb where it continues its development into a living embryo. In this way, genes that influence neuronal migration during development or specific interactions between

neurons can be studied in a natural environment, the growing embryo, rather than in artificial environments like tissue cultures. This technology promises to revolutionize our understanding of subtle developmental processes and could prove indispensable for understanding the normal development of neuronal connections.

Neuroscientists are also exploring the biochemistry of brain glycoconjugates—large molecules made of many sugar subunits linked to other biological compounds—to determine the specific roles that these cell surface molecules might play in directing the formation of neuronal pathways. Recent work on lectins in the nervous system suggests that these carbohydrate-binding proteins may interact with glycoconjugates on the surface of neurons and glia to help organize neuronal networks.

Extracellular and cell surface glycoconjugates have been known for a long time, and their position on the cell surface has been thoroughly documented. However, no one knows what they do. Researchers have had difficulty in studying them because they are not synthesized directly from DNA, as is the case with proteins, but are assembled by the cooperative interaction of a group of enzymes, the glycosyltransferases. As new technologies, including mass spectroscopy, are developed with which to analyze their structure, and as more proteins that bind specific glycoconjugates are discovered, researchers will increase their study of these complex carbohydrates and discover their function in nerve growth and development.

Secrets of brain development unfolding. Future for mental health promising.

During the next decade, neuroscientists expect to find the factors that determine how neurons differentiate, leading to the many different subtypes or specific neuronal branching patterns seen in the brain. They should also identify the macromolecules that guide a neuron's axons and dendrites to their destinations, as well as the factors controlling neuronal death, a process critical during both development of the nervous system and its later aging and deterioration.

As researchers find mutants that influence the development of the nervous system, they will also isolate the gene products these genes encode. It will be common to find genes that are important in development, find out what protein they produce, clone the genes, make antibodies to the gene product, stain cells with the antibodies thereby identifying them, and then determine the function of the protein. The study of the interactions of genetic and extragenetic information is a new area currently receiving intensive study. There is now evidence that extragenetic information including information outside the organism (environment) is important in development and adaptation.

The Changing Nervous System

One of most important discoveries of the past decade is that the brain is constantly changing in response to a number of factors. For example, it is now clear that behavioral modification resulting from learning is

The brain changes constantly with experience.

associated with functional changes in the connections between nerve cells. These changes can be subtle, as when dendrites and axons are modified. More dramatic changes can occur, too, as when new neurons form in adult brains, a phenomenon now documented in fish, birds, and some mammals. In some cases, the newly generated neurons even replace older neurons. Disorders in the maintenance of the neurons once proper connections have been established might contribute to the onset of devastating mental diseases.

Molecular representation of memory.

A main paradigm for studying the brain's ability to change is learning. The belief that learning takes place in the whole brain was prevalent between 1940 and 1960. Thus, the size, not the site, of a brain lesion was thought to be responsible for the amount of learning impairment accompanying brain injury. This view has changed. Scientists now appreciate that, despite its enormous complexity, the brain is really an array of neurons organized into circuits. Different circuits process different kinds of information, and they do so in different ways. Only a subset of brain circuits is likely to be involved with the acquisition of specific new information. When the performance of these brain circuits changes as a result of prior experience, such changes constitute learning.

Memories first form at the synapses.

Researchers are giving much attention to the question of just how and where experience-dependent circuit changes take place, because that is how and where memory is stored. The common sea slug has been an ideal animal for this kind of study, because it has large neurons and a relatively simple nervous system. The results of these experiments suggest that experience-dependent chemical changes occur first in the synapses and can last for days or weeks, modifying the effectiveness of information flow between neurons. Researchers believe that these changes constitute the molecular representation of memory.

Work from several laboratories, however, also suggests that individual synapses are, quite often, short lived, surviving for at most a few weeks. This observation suggests that synapses may not be safe places to store long-term memories that last months and years. But if long-term memories are not stored in synapses, where? Perhaps in the nucleus of cells, in the chromosomes that contain the genetic information.

One of the major advances during the next several years will be in determining how short-term memory becomes long-term memory. The difficult task of showing how changes in synapses can produce long-term changes in the workings of a cell will entail learning how cellular events can regulate genetic expression. This means understanding how cells regulate gene expression in general, and in turn, how gene expression and behavior affect one another. The impact of these findings will reverberate throughout all of neuroscience.

Researchers have already uncovered a chemical mechanism that may explain how mammalian nerve cells change during memory formation. Several investigators had noted that when neurons were given brief but

intense high-frequency stimulation their electrical properties were changed in ways that would fit those proposed for memory: the changes were triggered by an electrical event, they were strengthened by repetition, and they persisted indefinitely. Researchers named this effect long-term potentiation, because the electrical properties of the affected nerve cells were altered for a long time.

A series of chemical reactions consititute memory.

Since this revelation, researchers have discovered a series of chemical reactions that produce the changes in neurons associated with long-term potentiation. These neurons use the neurotransmitter glutamate, an amino acid. The scientists found that intense high-frequency pulses trigger an unusually large release of calcium in the postsynaptic cell, which activates an enzyme that is dormant most other times. This enzyme, called calpain, degrades a protein, called fodrin, that is a major structural component of the synapse area in neurons.

When fodrin disintegrates, the cell changes shape, uncovering extra receptors for the neurotransmitter glutamate. The receptors appear to be present normally in the cell, but are buried in the cell's membrane. When the cell changes shape, the receptors rise to the membrane's surface. With more glutamate receptors on the synaptic surface, the postsynaptic cell becomes more responsive to glutamate released by its presynaptic partner. This, in turn, enables more calcium ions to enter the cell when glutamate binds to its receptor.

Other researchers recently discovered that the anesthetic ketamine, which causes severe amnesia, selectively blocks the flow of calcium into nerve cells. This not only supports the hypothesis for a molecular memory mechanism, but it also suggests a possible therapeutic approach to memory disorders: synthesize drugs that facilitate the entry of calcium into neurons. Such a drug might be of great value for patients with Alzheimer's disease, for example.

The chain of events involving calpain, fodrin, and other molecules is a plausible candidate for a memory mechanism because it occurs in the synapses in response to a physiological event, changes the responsiveness of the synapse, and is permanent. Furthermore, calpain is found only in those regions of the brain that are known to be involved in memory. Interestingly, calpain is also found in high levels in every area of the brain affected by Alzheimer's disease, a disorder most noted for its memory loss. The next step in this research will be to isolate the genes that code for calpain, fodrin, and the glutamate receptor. Investigators will then be in a position to study how cellular events can affect the expression of those genes.

In the near future, investigators will discern other molecules—receptors, neurotransmitters, structural proteins, and genes—involved in forming new neural connections in the adult brain. With this information, they will be able to identify problems involving these molecules and determine whether such abnormalities are related to mental illness. For example, if the brain must form new connections to

work properly, some mental disorders may be caused by increased or decreased synapse-forming activity. If such a connection is established, knowledge of the molecular basis of these processes should suggest plausible therapies for the disorders.

The changes associated with memory are one kind of synaptic plasticity, a term neuroscientists use to describe the malleability of the brain. Another form of plasticity might be the wholesale replacement of neurons, a process previously thought to be impossible. Support for this remarkable idea comes from studies of song birds, like canaries.

Adult brains can produce new nerve cells.

Neuroscientists were interested in seeing if the brains of male canaries changed when they learned a new courting song each fall. Male canaries start singing when they are 1 month old. Earlier work established that as they learn and their song develops, a region in the front part of their brains, called HVc, grows. Some neurons in HVc respond to sound, while others activate the bird's voice. By the time the canaries become full-blooded crooners, the HVc region has become eight times larger than it was at age 1 month. Furthermore, birds the researchers judged as being better singers had larger HVc areas.

The researchers designed experiments to test whether this extra growth was related to the formation of new synapses or entire neurons. To distinguish between these two possibilities they injected birds with radioactively labeled thymidine, which the brain can convert to thymine, one of the four nucleic acids in DNA. If nerve cells merely make new synapses, they will not make new DNA. But if new neurons form, those already in the HVc region will have to reproduce, making new DNA and using the radioactive thymine.

To their surprise, the scientists found that not only were new neurons being made in the HVc region, but they were reproducing so fast as to double in number in 7 weeks. Furthermore, many of these new neurons responded to sound, and others were active while the birds sang. Even more remarkable, these extra neurons die when the male canary stops singing after mating season, and new ones take their place every fall when the new song is being learned. Furthermore, scientists have now found that new neurons grow and die throughout the canary's forebrain in both males and females, although females do not have a major song repertoire. Similar genes may govern these processes in all vertebrates. If so, adult mammals might have these genes at their disposal.

Turning on and off genes that control nerve growth.

Over the next decade, researchers will learn how these genes are regulated, and whether the same processes occur in mammals. If neuroscientists can learn how to control these genes in adults, they will have discovered a splendid mechanism for brain self-repair.

As further experiments elucidate the mechanisms of plasticity, new understanding of mental illnesses will be apparent. For example, many believe that the fundamental problem in phobias is one of learning—somewhere along the line, a phobic learned to connect a particular

situation with fear. Discovering how learning occurs—and how "unlearning" occurs—could lead to improved treatments for these disorders. Most recently, several lines of evidence have suggested that autism may be related to problems involving neural learning circuits. When further work pins down this relationship, it will signal the opening of a new line of research into the causes of this disorder.

Communication Between Neurons

The task of the nervous system is to receive, send, process, store, and retrieve information, all accomplished through the basic unit of the brain, the neuron. Within a given neuron, signals are transmitted by waves of electrical activity caused by local changes in the permeability of neuronal membranes to ions. Upon reaching the terminal of a neuron, these electrical signals cause the secretion of one or more neurotransmitters, which diffuse across the narrow gap, or synapse, separating one nerve cell from the next. On reaching the other side of the synapse, the chemical transmitter acts on a receptor to either increase or decrease the probability that the next cell will transmit a signal and thus continue the flow of information. Whether such a signal is initiated is determined by the sum of all the influences impinging on that next cell.

The synapse, the focal point of brain function.

Thus, the synapse serves as the focal point for collecting and integrating information coming in from other nerves as well as from more distant sites that contribute signals to the extracellular space. In this way, hormonal and nutritional factors, as well as drugs, can affect the nervous system.

Studies carried out over the past decade have revolutionized our thinking about synaptic transmission. While it once was believed that only a handful of compounds were responsible for synaptic transmission, we now know that more than 100 such compounds exist. These transmitters can be divided into at least two classes. Some transmitters can be used to carry information at high frequency with great fidelity, as would be required in pathways that carry primary sensory information. Other transmitters, neuromodulators, operate more slowly and serve to modulate the actions of the first class, neurotransmitters. Often neurons contain more than one transmitter. Current research deals with identifying these transmitters, determining their anatomical location, and exploring their mechanisms of action and interaction.

Crosstalk at the synapse.

New insights have arisen in our understanding of how synaptic transmission is regulated. Neuroscientists long assumed that synaptic transmission operated in only one direction, with transmitters, released by one nerve at its terminal ending, acting on the next cell. The only receptors that had been identified were on the postsynaptic side of a synapse. Recently neuroscientists have learned about two types of presynaptic receptors—autoreceptors and heteroreceptors. Autoreceptors on a nerve receive signals from the transmitter released

by that nerve. Heteroreceptors receive signals from other transmitters, including those released from the postsynaptic target cell. Thus, autoreceptors tell a nerve what it said, while heteroreceptors tell a nerve what it heard.

Synaptic homeostasis may be crucial for nervous system health.

The functional significance of these feedback mechanisms is currently being examined. One possibility is that these mechanisms provide the information necessary for maintaining synaptic homeostasis, i.e., keeping the level of synaptic transmission constant. Synaptic homeostasis might be useful during development and aging. Throughout the first decade of life, the human brain develops gradually. Some processes, such as peak intellectual performance, must await full development, while other functions are relatively well established at an early age. Synaptic homeostasis might serve to maintain an adequate level of synaptic transmission until innervation is complete.

The same homeostatic mechanisms might be useful later in life as the process of development reverses itself and nerve cells begin to die. Synaptic homeostasis might also help the nervous system compensate for injury and thereby permit recovery of function after brain damage. These and other possibilities will be explored in years to come.

Another fruitful avenue of research concerns the synthesis of neurotransmitters inside the presynaptic neuron. Sometimes, a dramatic increase in synaptic transmission is desirable, as when the nervous system must deal with an abrupt alteration in the environment. Under such conditions, nerves must rapidly adapt and provide and receive signals at a very different rate. Among the many changes required is an increase in the rate of transmitter biosynthesis so the nerve can release transmitter more rapidly without depleting its store. Researchers now know that the rate at which a transmitter is synthesized is indeed coupled to the rate of its release. This involves the capacity of the genetic machinery of a nerve to turn on the production of specific proteins in response to changes in neuronal activity. How these events occur is the subject of major investigation among neuroscientists.

Surprising find: Nerve cells use multiple neurotransmitters.

Researchers recently discovered that neuropeptides can coexist and be coreleased with established neurotransmitters such as acetylcholine, biogenic amines (dopamine, noradrenaline, serotonin), and amino acids (GABA, glycine) from a single neuron. This newly found mode of regulation of transmitter processes requires reevaluation of the process of information transfer at the synapse.

Neuropeptides can be reasonably assumed to perform several different functions, some involved in modifying the chemical transmission process at a fast or semifast level, others having a longer modulating role, and still others influencing fundamental processes such as growth, development, differentiation, and axonal guiding. Recent evidence also suggests that neuropeptides and classical transmitters are not the only possible combinations for coexistence. Several classical transmitters,

for example, biogenic amines and amino acids, may also coexist in neurons. In light of this knowledge, the chemical signaling process is obviously more intricate than originally thought and should permit great specificity and precision of synaptic interactions.

Studies in different species indicate that transmitter coexistence has been preserved throughout evolution, a sign of functional importance. Efforts are currently underway to explore the physiological significance of coexistence as well as its role in pathological states. Modern molecular biological techniques give scientists new opportunities for analyzing the location and functional significance of coexistence. This should provide us with additional target sites for drugs to treat illnesses.

Cotransmission: Relevance to schizophrenia.

Currently, the dopamine-cholecystokinin coexistent neuronal system is being investigated for its relevance to schizophrenia. The dopamine hypothesis of schizophrenia states that the function of discrete mesotelencephalic dopamine neurons are altered in this disorder. Immunohistochemical studies revealed the presence of the peptide cholecystokinin in diverse areas of the brain, and cholecystokinin coexisting with dopamine in some neurons and displaying transmitter-like properties. These observations have generated considerable interest in the functional role of the coexistence of these compounds.

Electrophysiological studies demonstrate that locally applied cholecystokinin alters the activity of dopamine cells in the substantia nigra and produces excitatory effects on neurons in a brain region that contains coexistent cholecystokinin-dopamine neurons. Furthermore, acute systemic administration of cholecystokinin was shown to increase the firing rate of midbrain dopamine neurons. Based on physiological and biochemical studies, cholecystokinin appears to modulate the actions of dopamine primarily in those neuronal regions in which it coexists with dopamine. Thus, a potent and specific agonist or antagonist affecting the central cholecystokinin receptors might be a useful tool in further evaluating the role of the dopamine-cholecystokinin coexistent neurons.

Behavioral studies are currently investigating the functional significance of cholecystokinin-dopamine coexistence, and testing hypotheses suggesting that cholecystokinin mimics the behavioral actions of dopamine and/or potentiates or inhibits the actions of dopamine.

Ion channels: A fundamental unit of nerve activity.

Neurotransmitters and their receptors are but one part of the neurotransmission puzzle. An equally important component is the ion channels whose action actually propagates a nerve signal. An ion channel is a voltage- or chemical-sensitive protein located in the membrane of a nerve cell. Each nerve cell has 10 to 20 different types of ion channels that determine the electrical responsiveness of the nerve cell. Different classes of nerve cells have different complements of ion channels, and these channels are located at different sites in the

neuron. Thus, the various mixtures of ion channels determine the electrical personality or nerve cell type as well as the output of a given cell.

Researchers have made substantial progress in the past few years developing techniques to record the tiny electrical signals from single nerve cells and even single ion channels. Nerve signals can be recorded from both living animals and isolated single cells. Using these methods, neuroscientists have been able to study how ion channels respond to various stimuli, such as the presence of a particular ion, neurotransmitter, or a toxic molecule. One such study, for example, found that only about half of the dopamine neurons in the midbrain region are spontaneously sending nerve signals at any one time. This raises the possibility that in some disorders, such as schizophrenia, more dopamine neurons may be firing at a given time than are needed. If this should be true, then drugs that reduce this hyperactivity among dopamine neurons might prove useful in treating schizophrenia.

Internal messengers, a target for therapy.

In studies with isolated cells, investigators found that voltage-sensitive ion channels are also affected by activation of neurotransmitter receptors distinct from the ion channel itself. Since the receptor and ion channel are located at different sites in the neuron's membrane, the nerve cell must use an internal diffusible biochemical messenger to relay the information from the receptor to the ion channel. Because diffusion inside a cell is a slow process, this type of action can last for many minutes, in striking contrast to the better-known form of synaptic action that takes less than a second. Further study of this process showed that many different types of neurotransmitter receptors can use the same internal biochemical messenger and therefore activation of these different receptors will ultimately affect the same voltage-sensitive ion channels. This finding should allow researchers to design drugs targeted at steps involving these internal messengers, which could prove to be yet another therapeutic approach to treating behavioral disorders caused by inappropriate neurotransmission.

Future will reveal complete mechanism for nerve cell communication.

Neuroscientists have come to realize that synaptic transmission is much more complex than previously suspected. It involves many more chemical substances, many different types of receptors, and seems to operate with almost every combination and permutation of transmitter and receptor possible. Moreover, the transmission process is under a variety of regulatory influences. Some of these influences keep transmission under control, while others permit neurons to operate at a variable rate without running out of transmitter. Having begun to define the complexity, neuroscientists are now in a position to try to understand it and to apply that understanding to future experiments. For example, although the functional impact of a given transmitter usually is examined by administering that transmitter alone, future studies will examine multiple transmitters acting simultaneously on a nerve cell.

In the next decade, effort will be placed on developing new drugs that interact with receptors for classical neurotransmitters and

neuropeptides. The most rational approach to the development of new drugs requires information about the structure of the entire receptor and specifically the part of the receptor that binds the peptide. This information can be obtained by using techniques of molecular biology such as cloning the genes for the various peptide receptors. Several neurotransmitter receptors have already been cloned. These include the ß-adrenergic, the muscarinic M_1 and M_2, and the GABA receptors. From knowledge of the gene sequence, researchers can deduce the amino acid sequence of the receptor. Point mutations of the gene then allow replacement of single amino acids in the structure of the receptor. By injecting the messenger RNA (mRNA) of the mutated gene for the receptor into cells that do not have the receptor but can synthesize this receptor from the mRNA, researchers can pinpoint the part of the receptor that binds neurotransmitter.

More knowledge about synaptic transmission equals better therapies for mental illnesses.

With knowledge of the active binding site of the receptor and data on structure-activity relationships for a series of chemically related compounds that bind to this receptor, the investigator, using computerized molecular modeling, can construct the active site of the receptor and fit compounds into this site. This research should make possible the design of nonpeptide compounds that bind to the receptor and are able to penetrate the brain. This task requires enormous effort on the part of chemists and biochemists, first to synthesize the compounds and then to test them in various assays of receptor binding and function. Murine neuroblastoma clone N1E-115 as well as other cell types in culture can be used to screen for activity of the newly synthesized compounds. Any one of these new compounds could be a new psychotherapeutic drug.

Molecular modeling of the active receptor site.

The extent to which results obtained in the laboratory can be generalized to the real world has become an increasingly important concern. Thus, some investigators will carry out their measurements under simplified conditions, such as in nerve cells isolated in a tissue culture, while others will be studying the brains of freely moving animals using a new generation of microsensors capable of measuring the levels of neurotransmitters in individual synapses.

The bottom line of this research will be improved therapies for mental illness. With the techniques currently available for monitoring the behavior of individual brain cells, our understanding of the mechanism of action of commonly used psychotherapeutic agents should proceed at a much faster pace, leading to the design of new and more effective medications.

Such research will also change the medical community's idea of the type of drugs useful for the treatment of mental illness. Most of today's psychotherapeutic medications act on the surface of nerve cells, affecting either the receptor or the amount of neurotransmitter present at the synapse. Now that neuroscientists know that most neurotransmitters use internal messengers to carry the signal throughout the nerve cell, drugs will probably be developed that bypass the surface membrane receptor and interact inside the nerve cell on

internal biochemical messages. Such drugs will be valuable tools in furthering our understanding of neurotransmission and, in fact, may be clinically efficacious.

New ways of administering drugs.

The manner in which drugs are administered will also change in the future. Medications taken by mouth or intravenously act on all regions of the brain. As a result, effects can occur on all sites that use the particular neurotransmitter with which the drug interacts. This source of undesired side effects might be minimized by the application of medications via small catheters to the specific affected site or by linking the drug to a molecular carrier that, even when administered peripherally, will carry the drug to the brain region where its therapeutic action is exerted.

Further down the road, neuroscientists will be able to relate the action of neurotransmitters on specific neural circuits to behavior, cognition, and emotion. Investigators can already record the electrical behavior of individual cells or the release of neurotransmitter from specific neural circuits in a behaving animal. Developing compounds with specific actions on well-defined neurotransmitter systems and their administration to specified neural circuits will help unravel the means by which neural circuits control behavior. This should contribute to the development of more sophisticated animal models of human mental illness, permitting the more accurate testing of psychotherapeutic drugs.

Where Emotions Arise

Neuroanatomy of emotion.

Once it was popular to imagine the brain as having a number of centers—feeding center, sleeping center, etc.—devoted to various behavioral functions. The modern approach is to view the brain as a collection of interconnected circuits that control various aspects of behavior. The goal of functional neuroanatomy research is to unravel the complex components that make up these circuits and to understand the mechanisms by which each component of a circuit communicates with the next link in the circuit to produce particular behaviors. Neuroscientists have already made tremendous progress in determining the functional neuroanatomy of large parts of the brain. A great deal is now known about the network involved in emotion.

Life's experiences are colored by the emotional state of the organism, as shown by many studies of the profound influence of mood on the quantity and quality of what is remembered about a given experience. Moreover, the emotional tone of an experience can be remembered when no other details can be recalled. As learning theorists have long recognized, emotionally charged stimuli play an important role as reinforcers in the establishment of memories.

Over the past decade, researchers have found that the sensory organs—the eyes and ears, for example—transmit information to defined brain regions. Within each system, sensory information travels from the

periphery to the thalamus and then to specific areas of the cerebral cortex where the highest levels of sensory and perceptual processing occur. Anatomical studies have shown that each sensory system of the cortex has connections with the limbic system, an area of the brain long viewed as essential in the mediation of emotion.

Amygdala crucial to processing emotional information.

Of particular importance are connections linking the sensory areas of the cortex with the part of the limbic system called the amygdala. Visual stimuli are given emotional salience by a series of projections that run through the visual thalamus to the primary and secondary areas of the visual cortex and then to visual areas of the temporal lobe. The latter regions have connections with the amygdala. Interrupting the flow of information from the visual areas of the cortex to the amygdala, but not to other limbic areas, disrupts emotional processing. Animals with amygdala lesions are deficient in learning and remembering new information about the significance of visual stimuli; for example, stimuli once feared are treated indiscriminately.

Recent experiments that recorded the electrical activity of neurons in the amygdala and the cortical areas that project to it also demonstrated the importance of these connections to emotional processing. Cells in the visual regions of the cortex respond to the sensory properties of visual stimuli but are not sensitive to the affective value of the stimuli. In contrast, cells in the amygdala, as well as cells in areas to which the amygdala sends fiber projections, respond to the affective qualities but not the sensory properties of visual stimuli. The amygdala, then, appears to be a pivotal limbic structure involved in the processing of the emotional significance of sensory stimuli transmitted through the visual cortex. Although researchers have done less work with the other senses, it appears that projections to the amygdala from the auditory, somatosensory, and taste areas of the cortex play similar roles.

To date, work in determining the functional neuroanatomy of emotion has concentrated almost entirely on locating the anatomical pathways involved. Researchers have learned, for example, how the brain receives and evaluates the emotional meaning of sensory inputs, controls emotional responses on the basis of the emotional meanings processed, and is affected by feedback from the expression of emotional responses. The identification of those circuits involved in emotional processing opens the way for new studies of the action of clinically effective drugs and for the development of new drugs.

With circuits in hand, research now turns to studying biochemistry of emotion.

With an idea of the critical circuits involved, neuroscientists can then study the effect of drugs on the known circuitry. For example, the site of action of orally administered benzodiazepines in relieving anxiety in humans is unknown. Benzodiazepine receptors are located in many different regions of the limbic system, as well as other areas of the brain. However, researchers found recently that benzodiazepine receptors are highly concentrated in a particular part of the amygdala critical to emotional processing, suggesting that this structure may be an important site of their action. Given that this is also the sensory

receptive region of the amygdala, these observations suggest that these drugs reduce anxiety, at least in part, by controlling some of the sensory stimuli that can activate emotional networks. Studies are now underway to explore this connection further, which should provide new insights into the tie between sensory stimuli and emotions such as anxiety.

Expression of emotion, a clue to schizophrenia.

Another avenue of research with considerable promise involves identifying the pathways underlying the expression of emotional responses. For example, researchers are beginning to examine how the brain controls the facial muscles when expressing emotion. Anatomical studies are beginning to identify specific pathways by which information processed in the amygdala and possibly other forebrain regions control the facial nerves. The significance of this work for mental illnesses lies in the importance of facial expression for humans and other primates in communicating emotion. In fact, a disturbance in the expression of emotion is the hallmark of some forms of schizophrenia. Thus, understanding more about the regulation of emotions will provide important clues about the pathophysiology of this illness.

Emotion and learning may be intertwined.

Emotional experience clearly involves functional interactions between learning and emotional systems. Of special importance to these interactions may be specific pathways between the amygdala and structures such as the hippocampus and cortex, which are both involved in higher cognitive functions. Since it is difficult to assess emotional experience and learning in most animals, these studies will have to be done in primates or human volunteers using techniques such as positron emission tomography or magnetic resonance or neuromagnetic imaging.

For the last 40 years, the limbic system has been considered the universal emotional system of the brain. This view is being challenged today. The limbic system appears to be involved in cognition as well as in emotion. The brain may contain a specific emotional system, but researchers have studied too few types of emotions to draw any precise conclusions from present data. Future studies will examine the contribution of many different brain areas, particularly those areas traditionally included in the limbic system concept, to a variety of emotional tasks. A universal system would be involved in the mediation of emotional responses evoked through any sensory system and involving all emotions (e.g., love as well as hate, desire as well as fear). Whether investigators will find such a general system or whether each type of emotion is separately represented remains to be discovered.

Once neuroscientists understand the neural mechanisms of emotional information processing, they will be able to approach disorders of emotional information processing more wisely. The present opportunities in this area are perhaps greatest for phobic, anxiety, and panic disorders. Experiments in animals have begun to identify the neural circuits involved in fear. Anxiety, phobia, and panic, being

instances of fear out of control, may involve processing abnormalities in the circuits of fear. If the locations of abnormal processing can be determined and the neurotransmitters involved identified, new and specific treatment strategies might be suggested. Similar opportunities are possible for other aspects of mental illness.

The neuroanatomy of fear—understanding anxiety, phobias, and panic.

Detailed knowledge of the anatomy and chemistry of systems in the brain that mediate reinforcement is another path to the long-term goal of finding more effective treatments for serious psychiatric disease. An impaired ability to experience pleasure or reward is the single most important and invariant feature of major depressive illness. Understanding the systems in the brain that mediate reward processes is fundamentally important, because dysfunction of these systems may well be the cause of this common and devastating psychiatric disease.

Neuroanatomy of pleasure, a clue to depression.

The search for the neural circuitry of reward began approximately 30 years ago with the discovery that an animal will work to stimulate certain parts of its brain with electrical current; this is called intracranial self-stimulation. Similar findings were subsequently obtained in humans who reported feelings of intense pleasure when discrete regions in their brains were stimulated with electrodes during brain surgery. Neuroscientists have since demonstrated that dopamine-containing neurons located in an area of the brain called the ventral tegmental area are critical for mediating the reinforcing effects of stimulation at this site. Researchers used a combination of behavioral and neurochemical techniques to show that intracranial self-stimulation significantly increases the rate at which dopamine is released and metabolized in the nucleus accumbens, an area that earlier anatomical and neurochemical studies showed to be innervated by dopamine-containing neurons arising in the ventral tegmental area.

Experiments from a number of laboratories have demonstrated that animals lose interest in and eventually stop intravenous self-administration of either cocaine or amphetamine when dopamine is removed from the nucleus accumbens. These findings not only provide another method for studying the neural circuitry of reward, but they serve as an animal model of human drug abuse. They also pinpoint the precise spot in the brain where these drugs of abuse produce their pleasurable effects. Such knowledge may lead to new strategies in the cure and prevention of drug abuse.

Drug abuse tied to brain's reward system.

The recent development of in vivo electrochemistry, brain microdialysis, and positron emission tomography provides researchers with new approaches to study brain function. In vivo electrochemistry and brain microdialysis provide the opportunity to understand the exact circumstances in the normally behaving animal under which dopamine release is either increased or decreased. Using these techniques, we can ask questions such as: Is dopamine release in the nucleus accumbens enhanced during the performance of behaviors that animals find highly reinforcing? Is this release influenced by procedures that produce animal models of depression? Can changes produced by such

procedures be reversed by antidepressant drugs? If so, this will provide for the first time an animal model on which completely new classes of antidepressant compounds can be tested. In a similar vein, now that animal studies have clearly identified a region in the brain that is closely tied to reward processes, researchers will be able to use positron emission tomography to conduct studies in humans to determine if the metabolic activity in the nucleus accumbens is abnormal in depressed patients.

New ways to influence behavior through the brain's reward system.

Neuroscientists should also be able to determine the exact inputs to the dopamine neurons that mediate reinforcement. Similarly, they should be able to identify and understand the characteristics of the target neurons that the dopamine neurons innervate. This will be the first step in elucidating the complete circuitry of the reward system of which the dopamine-utilizing neurons are but one component. Once the inputs and outputs are known, the next step will be to determine the neurotransmitters that they contain.

Given this body of information, it will then be possible to make rational judgments about the manner in which the overall activity of the circuit could be influenced by novel drugs. For example, some of the newly discovered neuropeptides are known to influence the activity of the dopamine-containing neurons. Thus, analogs of these peptides, which could be designed to cross the blood-brain barrier, might be useful in the treatment of various conditions in which dopamine system malfunctions have been implicated, such as schizophrenia, Parkinson's disease, and depression.

Apart from the pharmacological approach, it would also be valuable to determine the circumstances under which the activity of the dopaminergic neurons is either increased or decreased by environmental stimuli. Such stimuli might then be used either alone or in combination with pharmacological agents in the treatment of major depressive illness.

Mapping receptors marks key advances.

An important component of all such studies will be mapping the various molecular systems—neurotransmitters and receptors, for example—that are found throughout the brain. Mapping implies more than simply measuring or detecting these molecules; it means measuring and locating them in the brain at the same time. Knowledge of the location of the receptors provides neuroscientists with significant information, because different parts of the brain are related to very different functions. Moreover, the mapping can be done at the microscopic level so that these receptors can be localized with great precision. While dozens of receptors for drugs and brain chemicals have been studied so far, new receptors remain to be discovered and examined. This in turn will reveal yet additional information about both normal and diseased brains.

The two main approaches to receptor mapping are in vivo mapping and

in vitro mapping. In vivo receptor mapping involves tagging receptors with a radioactive compound administered systemically in the living organism. The distribution of the tagged receptors is studied in the living animal by positron emission tomography, or the animal can be sacrificed, the brain removed, and the distribution of receptors studied by autoradiography. With this technique, tissue sections with tagged receptors are pressed against special photographic emulsions so that the location of and quantity of radioactivity in the different sections can be localized or imaged on the developed film.

In vitro mapping takes tissue sections from nonliving animals or humans and incubates them in nutrient media so that the receptors can be tagged with radioactive compounds. The distribution of the receptors is then determined by autoradiography.

Within the next 5 years, mapping studies will reveal which neurotransmitter systems and which neuronal populations are involved in a variety of specific behavioral disorders. This information will produce a more detailed understanding of diseases such as schizophrenia and depression, and neurodegenerative disorders like Alzheimer's disease. As new discoveries are made, new treatments will be suggested. For example, if these studies show that certain biochemicals are depleted in certain disease states, then replacement therapies can be attempted. Such replacement therapy has proven very successful in Parkinson's disease.

A very important prospect for the future is the application of this mapping approach to the visualization of many other important biological molecules in the brain. These include enzymes, various storage sites for endogenous biochemicals, and molecules involved in other processes such as membrane transport mechanisms. Neuroscientists will discover how to tag these important molecules and then map them. Just as with receptors, these other sites will be explored to produce some understanding of their function in the normal state as well as their dysfunction in disease states.

Mapping diseased brains.

In the more distant future, neuroscientists will develop a wide range of detailed, precise maps of the normal human brain and, ultimately, similarly precise and detailed maps of the human brain in various disease states. These maps will tell us how these diseases affect different parts of the brain and may suggest treatments for these diseases. Receptor mapping will become a routine tool, providing new information on the pathology of various diseases at the microscopic level. Procedures for producing receptor maps will be automated so that computers will analyze the maps, classify the data, compare the data to normal and disease states, and alert investigators about significant changes. In vivo receptor mapping will be improved to the point where positron emission tomographic scanning of receptor distributions will become routine and an important diagnostic tool for neuropsychiatric disorders.

Responding to the Outside World

How the brain pays attention.

The human brain's capacity to process information is limited. We cannot, for example, follow several conversations at the same time, read more than a few words on a page at a time, or recognize every face in a crowded room at the same instant. Likewise, we cannot simultaneously think two thoughts or recall multiple memories.

In each of these examples, the brain is confronted with multiple demands on its resources, demands that must compete for further processing and conscious awareness. Some of the demands are external, such as visual and physical sensations, whereas others are internal, such as stored memories and the near infinity of potential thoughts. The brain, therefore, requires a mechanism to select which particular demand achieves preeminence at any given moment. This is what we call attention.

Given the central role that attention plays in organizing both thought and behavior, it is not surprising that attention defects are associated with many different mental diseases and behavioral disorders. For example, when recovered schizophrenics describe their thought process while they were psychotic, they often recount how thoughts, feelings, perceptions, and memories intruded upon one another. People suffering from depression complain of their inability to concentrate, and hyperactive children have difficulty sustaining attention for more than a few moments and are easily distracted. Whether attention problems are a cause or an effect of a mental illness, future understanding of the neural basis of attention could provide an effective basis for treatment of such disorders.

Brain waves can measure attention process.

Many studies of attention rely on measuring what researchers call event-related potentials. External stimuli activate large numbers of neurons in the sensory pathways and higher brain centers, where the information is perceived, analyzed, and understood. These activated nerve cell populations produce electric field potentials that spread through the brain and can easily be recorded from the intact scalp. The potentials evoked in this way have a time course and anatomical distribution that depend upon both the type of stimulus and the nature of the perceptual and thought processes it triggers. Since many of these electrical waves are coupled to internal psychological events provoked by the stimulus, they have been termed event-related potentials, and measuring them represents one way that neuroscientists are studying how the brain pays attention to the outside world.

Neuroscientists have now accumulated a substantial body of evidence showing that event-related potentials are reliable measures of stimulus selection processes under appropriately controlled conditions. For example, the principal electrophysiological effect of attending to a message (such as a given speaker's voice in one ear) is to enlarge an early negative event-related potential (recorded signals can have either a positive or negative voltage). The negative potential increases as the

subject pays greater attention to the relevant channel of sounds, and it appears to be a neural sign of the detailed analysis of the relevant stimulus features. This effect is associated with a relative suppression of irrelevant environmental inputs at an early stage of processing, thereby protecting higher centers from sensory overload.

Much of the work in studying attention has concentrated on how the brain processes competing visual signals arriving in the cortex. When visual information reaches the cortex, it splits into two major pathways—one dips down into the temporal regions (just above the ears) and the other shoots up into the parietal region (at the back of the top of the head) and certain parts of the frontal region. The temporal pathway contains the cortical areas responsible for analyzing the patterns on the retina and identifying objects. In contrast, the parietal pathway seems little concerned with what objects are, but rather with where objects are located. The parietal system is also critically involved in the ability to shift attention from one location to another.

Parietal cortex shifts attention from one thing to another.

People who have suffered brain damage due to trauma or disease in their parietal cortex provide the most striking evidence that the parietal system is involved in the ability to disengage attention from one location and shift it to another. When a person with damage to the left parietal system (the part responsible for perceiving the right side of visual space) is confronted with two objects, the person's attention may become stuck on the object on the left side of the visual field while the object on the right side seems to disappear. The converse is true with damage to the right parietal system. Artists who have suffered damage to the parietal cortex on one side of their brain have been known to paint pictures with one half splendidly represented and the other half shrunken and distorted.

Individual neurons pay attention.

Neuroscientists have also observed the parietal cortex shifting attention at the level of individual parietal neurons. Using electrical recordings from the parietal cortex of rhesus monkeys trained to switch attention from one location to another, researchers found that parietal neurons give electrical discharges when objects are placed at specific locations within the monkey's field of view. The location covered by a particular neuron is known as the neuron's receptive field. When the monkey attends to an object located within the receptive field of a parietal neuron, the neuron gives greatly enhanced discharges, whereas if the monkey ignores objects at that location, the discharges are reduced. These enhanced discharges appear to be used by other parts of the brain to control perceptions of the attended objects as well as movements of the body towards them.

How do the discharges of parietal neurons control movement of the body and eyes toward attended objects? The answer may lie in long anatomical connections between the parietal cortex and the frontal cortex, which contains neural circuitry for planning motion. Neuronal recordings in monkeys show that neurons in a part of the frontal cortex discharge before the monkey makes certain eye movements toward

objects in its visual field. Moreover, these neurons fire only when the eye movements are deliberate, not random. Although much of the frontal cortex remains to be explored by electrical recordings, it presumably contains neural circuits underlying directed motion of other body parts in addition to those that influence the eyes.

The results from recent neuronal recording experiments in the prestriate and temporal cortex suggest that the control of the neurons involved in perceiving and remembering objects may work analogously to the control of neurons involved in movement. In contrast to either parietal or frontal neurons, prestriate and temporal neurons work together to recognize objects located within their receptive fields. Neurons in the prestriate cortex code object features, such as the length, width, and color of the individual parts, and pass this information on to large populations of neurons in the temporal cortex, which code global object properties, such as whether an object is a cup, a pencil, or the face of a friend.

Neural systems for selective attention.

For many years, a particularly puzzling problem was how prestriate and temporal neurons limit the amount of visual information they process. Many different objects will typically lie within our view, and many will fall within the receptive field of a given prestriate or temporal neuron. Yet, we are normally fully aware of only one or two objects at a time, usually the objects that are most important. How are neurons kept from processing unwanted information? The answer seems to be that the selective attention mechanism filters unwanted information from the receptive fields of prestriate and temporal neurons.

Neuroscientists have observed this filtering of unwanted information in individual neurons in primates trained on a visual recognition task. The primates were required to closely attend to objects at one location (without making any eye movements), while irrelevant objects were presented at a second. When both objects were within the receptive field of either a prestriate or temporal neuron, the neuron's discharge to the ignored object was strongly suppressed. Thus, neurons pass on information almost exclusively about attended objects to other neurons in the brain, explaining why we have little or no perceptual awareness of ignored objects.

Attention disorders may lie in damage to neural circuitry.

If research on attention processes continues on its present path, neuroscientists should be able to identify the brain structures underlying attention and provide a basic understanding of how they work at the level of neuronal networks. In addition, researchers will discover which neurotransmitters are used in these networks and how they are used by the attention mechanisms. With this information in hand, it will be possible to link specific attention disorders with specific dysfunctions in the brain structures underlying attention and perfect the technologies, such as event-related potential measurements, positron emission tomography or neuromagnetic imaging, to identify dysfunctional brain structures in patients.

Brain and Body Connection

The relatively new fields of neuroendocrinology and neuropeptide biology are the offspring of the burgeoning disciplines of endocrinology and neuroscience. Endocrinology is the study of the nature and action of hormones, substances that are secreted by endocrine organs directly into the blood stream where they act at distant sites. The hormones produced by endocrine glands such as the thyroid, pituitary, adrenals, testes, and ovaries exert important effects on the brain. Recently, neuroscientists discovered that the brain, too, is an endocrine organ, producing hormones that act on other organs and brain cells. Neuroendocrinology is the study of the synthesis, regulation, and action of these neurohormones.

The brain is a hormone factory.

In 1970, two groups of researchers discovered thyrotropin-releasing hormone, a peptide made in the brain and released into a specialized blood system, called the hypothalamo-hypophysial portal system, that connects the brain and the anterior pituitary gland. When the hormone reaches the pituitary, it binds to special membrane receptors and causes the synthesis and release of another peptide hormone, thyroid-stimulating hormone, which in turn is released into the general circulation. It travels to the thyroid gland where it binds to specialized membrane receptors and causes the synthesis and release of thyroid hormones. Thus, the brain controls the anterior pituitary gland which in turn controls the thyroid.

The concentration of thyroid hormone in blood regulates the secretion of both thyrotropin-releasing hormone and thyroid-stimulating hormone from the brain and pituitary, respectively, a phenomenon known as negative feedback. This tightly regulated system allows for the rigid control of this endocrine system in the body.

Since 1970, many other hypothalamic releasing and inhibiting hormones have been characterized and their structures determined. These include gonadotropin-releasing hormone (which controls the pituitary-gonadal axis), corticotropin-releasing factor (pituitary-adrenal axis), growth hormone-releasing factor (growth hormone secretion), and somatostatin, which inhibits the secretion of many pituitary hormones. These peptides enable the brain to serve as a master control on the body's endocrine system.

Master controller of body endocrine system.

Two major findings have served as a major impetus for subsequent study. First was the discovery that these releasing hormones are present not only in the hypothalamus, where they function as neuroendocrine regulators, but are also found in widespread areas of the brain and spinal cord. This finding suggests a role for these peptides in higher brain centers controlling movement and locomotion, body temperature, sexual behavior, appetite, thirst, and cognition. In addition, there is considerable evidence that these releasing hormones may be involved in illnesses such as depression, schizophrenia,

Alzheimer's disease, amyotrophic lateral sclerosis, anorexia nervosa, Huntington's disease, and Parkinson's disease.

Neuropeptides: Newest members of neurotransmitter family may provide key to many illnesses.

The second major finding was the presence of peripheral hormones in brain neurons. These neuropeptides (for example, insulin, angiotensin, calcitonin) apparently do not function as typical hormones but rather as neurotransmitters. Until about 15 years ago, neuroscientists knew of only 10 or so neurotransmitters, such as dopamine, norepinephrine, and acetylcholine. Now it is clear that, as a class, neuropeptides comprise a substantial percentage of neurotransmitters in the central nervous system, acting on as many as 50 percent of the synapses in the brain.

For example, work on the neuropeptide cholecystokinin, found in both the gastrointestinal tract and the brain, offers a good example of the research being done in neuroendocrinology. Investigators first discovered this peptide in the small intestine, where it is released when food enters the stomach. Scientists have known for some time that hormonal, and not neural, inputs to the gastrointestinal tract control satiety, and cholecystokinin appears to play a central role. It may be the long sought-after satiety hormone.

Cholecystokinin analogs may be useful in treating eating disorders.

In animals prepared with a gastric fistula, a preparation in which food that is ingested is not absorbed but collected in a reservoir, cholecystokinin administered in the space surrounding the intestines induces a clear inhibition of feeding. Other experiments have since shown that cholecystokinin inhibits food intake induced by stress and by a variety of drugs such as norepinephrine and muscimol. Researchers are now attempting to discover whether cholecystokinin secretion or cholecystokinin action at the receptor is abnormal in eating disorders such as anorexia nervosa, bulimia, or obesity. If so, cholecystokinin or a cholecystokinin analog might be useful in treating these disorders.

Neuroscientists are now mapping the distribution of cholecystokinin throughout the nervous system. This will give a clearer picture of the neural circuits involved in eating behaviors, for there are certainly higher brain functions associated with eating. For example, since people learn to like or dislike specific foods, there should be a link between circuits of the brain involved in eating behavior and memory. When these connections are better understood, then perhaps researchers will be able to develop procedures to treat eating disorders through modulation of brain regulatory systems.

Stress hormones isolated, linked with depression.

Six years ago, researchers succeeded in isolating the elusive corticotropin-releasing factor, a hypothalamic-releasing hormone that controls the secretion of adrenocorticotropin and beta-endorphin (two more neuropeptides) from the anterior pituitary. Adrenocorticotropin then acts on the adrenal glands to stimulate release of cortisol in humans and corticosterone in the rat. This hypothalamic-pituitary-adrenal system has long been known to be activated by stress. In recent

experiments, investigators showed that stress produces a distinct pattern of changes in regional brain corticotropin-releasing factor concentrations and, moreover, that clinically effective antianxiety drugs block these stress-induced changes in corticotropin-releasing factor and also block stress-induced elevations in the concentration of adrenocorticotropin and corticosterone in blood.

Researchers have now begun to study corticotropin-releasing factor's role in depression because stress is known to precipitate depression in vulnerable individuals and because approximately 50 percent of depressed patients are known to have a hyperactive hypothalamic-pituitary-adrenal axis. Several investigators have shown that when administered directly into the brain, corticotropin-releasing factor produces effects reminiscent of the symptoms of patients with major depression, including disturbed sleep, diminished appetite, decreased sexual behavior, and altered locomotor activity. Corticotropin-releasing factor also has antianxiety properties in rats. Based on these findings, neuroscientists have now hypothesized that depressed patients secrete too much corticotropin-releasing factor. If this idea is indeed correct, it opens a whole new arena of possible treatments for depression using drugs that inhibit the release or block the action of corticotropin-releasing factor.

Neuroendocrinology has also opened a new avenue of investigation in Alzheimer's disease research. Although much attention has been focused on the degeneration of acetylcholine-using, or cholinergic, neurons in Alzheimer's disease, treatment with drugs that purportedly enhance acetylcholine transmission have not proved particularly beneficial. Researchers have now shifted their attention to the recent discoveries that certain neuropeptide-containing neurons also degenerate in Alzheimer's disease. In particular, neurons containing corticotropin-releasing factor and those containing somatostatin, a 14-amino acid long peptide, are markedly reduced in the cerebral cortex of patients with Alzheimer's disease.

In addition, investigators have found both corticotropin-releasing factor and somatostatin within senile plaques, one of the pathological hallmarks of Alzheimer's disease. Recently, several groups demonstrated that drug depletion of brain somatostatin produces profound learning problems in rats. If further study confirms that these two peptides play central roles in Alzheimer's disease, then drugs that mimic these peptides may provide important new treatments for this disorder.

Neuropeptide deficits in damaged nerve cells implicated in Alzheimer's disease.

Within the next few years, neuroscientists will use the techniques of molecular biology to identify still other neuropeptides. Once identified, their physiological roles in the brain can be studied as well as their distribution in the normal and diseased brain. Many investigators believe that by the time all is said and done, the total number of brain peptides will reach nearly 200, making neuropeptides the largest class of neurotransmitters and neuromodulators in the brain, undoubtedly

accounting for neurotransmission at the largest percentage of synapses in the central nervous system.

In the meantime, investigators are studying the mechanisms by which neuropeptides work at the synapse. Very little is currently known, for example, about the termination of neuropeptide action after the peptide is released from the presynaptic terminal. Enzymes degrade neuropeptides into peptide fragments and finally into their constituent amino acids, but the specificity, location, and characteristics of these enzymes are unknown. Further research may reveal that some illnesses are caused by malfunctions in neuropeptide processing, which may, in turn, be caused by a mutant gene.

Using DNA probes, scientists will begin to study the relationship between neuropeptide genes and nerve function. By studying how these genes turn on and off, researchers will get a new insight into neuronal function and behavior. Within the next 5 years, improved analytical and imaging techniques will enable neuroscientists to measure the concentrations of neuropeptides in the brains of patients with autism, attention deficit disorder, schizophrenia, depression and mania, anxiety disorders, Alzheimer's disease, AIDS, tardive dyskinesia, and Parkinson's disease. These studies will determine the role of neuropeptides in the pathogenesis of these devastating disorders.

Other exciting developments will include purification and sequencing of neuropeptide receptors. These studies will allow researchers not only to identify neuropeptide receptors and possible variants in disease states but also to develop DNA probes to examine these genes' expression. In fact, if further investigations find that a deficient peptide or peptide receptor causes a disease, it should be feasible to develop therapies to remedy the situation.

Neurotoxins

One of the most powerful techniques for elucidating the behavioral and physiologic role of a defined group of neurons is to determine the consequences of their selective deletion in experimental animals. In this context, neurotoxins have assumed considerable importance in basic research on the role of specific neuronal pathways in mental illnesses.

Neurotoxins may cause disease and help discover disease processes.

Broadly speaking, a neurotoxin is any substance that can damage the nervous system. Many such substances are highly selective in their destruction, attacking the unique or defining characteristics of a specific type of neuron. Some neurotoxins take advantage of selective metabolic characteristics that cause certain neurons to concentrate the toxin, thereby poisoning them. Other neurotoxins can eliminate neurons on the basis of the time when the neurons are formed in the developing brain. A third important group of neurotoxins target the receptors of neurotransmitters in the brain; these substances literally excite neurons to death.

Within the past few years, scientists have found that neurotoxins can reproduce in experimental animals the chemical and structural abnormalities that occur in a number of disorders such as Alzheimer's, Parkinson's, and Huntington's disease. Thus, neurotoxins can provide powerful new experimental models for these disorders.

By clarifying the way these toxins work, neuroscientists expect to understand the pathologic processes that may account for the selective neuronal degeneration seen in humans. Selective neurotoxins are powerful tools for unraveling the mechanisms of neuronal communication in brain relevant to mental disorders. Studies of neurotoxin action may also provide fundamental insights into why certain neuronal systems are vulnerable in degenerative disorders.

One biochemical characteristic that has been particularly important for targeting neurotoxins to specific neurotransmitter systems is the high affinity uptake (transport) process of neurons. This process actively removes the neurotransmitter from the synapse to terminate its action. Several neurotoxins structurally resemble neurotransmitters or are metabolically converted to close analogs of neurotransmitters. The transport process, perceiving the toxin to be the neurotransmitter, avidly concentrates it within the neurons. The accumulated toxin thereby selectively poisons those neurons that release and accumulate the neurotransmitter.

One such toxin is 6-hydroxydopamine, which is closely related chemically to dopamine. A small modification renders the compound extremely labile: it decomposes inside a neuron and generates hydrogen peroxide, which is destructive to the neuron. After injection into the brain of adult experimental animals (or peripheral administration to neonates), 6-hydroxydopamine is rapidly accumulated by the high affinity transport processes on neurons that use dopamine or the structurally related norepinephrine as their neurotransmitters, thereby destroying them.

Injecting 6-hydroxydopamine into the substantia nigra, where dopaminergic cells are concentrated, reproduces well the biochemical and behavioral abnormalities associated with Parkinson's disease. Experiments using this technique have clarified the role of dopamine neurons in behavior and illuminated adaptive mechanisms that result from their elimination.

Neurotoxins identify the role that specific neural systems play in behavior.

Lesions of central noradrenergic neurons by 6-hydroxydopamine have shown the important role these neurons play in arousal and mood states and have identified them as an important site of action of many of the effective antidepressant drugs. The neurotoxin 5,7-dihyroxytryptamine, which causes toxicity by a mechanism similar to 6-hydroxydopamine, selectively destroys neurons that use serotonin as their neurotransmitter. This neurotoxin has contributed to our understanding of the role of serotonergic neurons in sleep mechanisms, aggression, and mood states.

Cholinergic neurons possess a high affinity transport process for choline, the precursor for their neurotransmitter. Chemists recently synthesized a highly reactive analog of choline that, when injected into brain, accumulates in cholinergic neurons. This produces irreversible destruction of their axons and dendrites. Lesions of cholinergic neurons innervating the cerebral cortex and hippocampus—areas involved in higher mental functions—reproduce certain aspects of the neurochemical abnormalities and the cognitive impairments that occur in Alzheimer's disease.

Parkinson's disease may result from environmental neurotoxin.

Intriguing studies with the toxin MPTP show the direct clinical relevance of neurotoxin research to the pathophysiology of Parkinson's disease. This substance, a byproduct in the illicit synthesis of the narcotic meperidine, causes the rapid development of Parkinson's syndrome in young adults who abuse home-made meperidine. Clinical studies and subsequent autopsy analysis of the brain of an affected young adult demonstrated the same symptoms and neuropathology, including the degeneration of dopaminergic neurons, that occurs in Parkinson's disease.

Studies on experimental animals indicate that MPTP itself is not directly neurotoxic, but rather is converted by an enzyme in the brain to the active neurotoxin MPP+, which accumulates solely in dopaminergic neurons. Researchers are now trying to determine whether inhibitors of that enzyme might slow the progression of Parkinson's syndrome.

Neuroscientists are also considering the hypothesis that Parkinson's disease, which does not appear to be an inherited disorder, might be caused by exposure to environmental contaminants, since MPTP resembles a large number of chemicals that occur in industrialized society. Also, inherited factors might determine the vulnerability of dopaminergic neurons to environmental toxins, so understanding the metabolic events that lead to toxicity could allow scientists to identify individuals who are risk for nerve damage. Uncovering such factors would also enable physicians to institute appropriate preventive treatments to circumvent the ultimate development of the disorder.

Early events in brain development affect later behavior in adults.

Another group of neurotoxins interfere with cell development. Epidemiologic studies reveal that prenatal brain damage is associated with markedly increased risk for psychiatric disturbance. In addition, structural abnormalities have been linked with disorders such as schizophrenia, obsessive/compulsive disorder, and autism. Since these structural deficits remain stable over time, they probably originate in the developing fetus. Thus, to understand better the developmental, behavioral, and synaptic neurochemical implications of such deficits, it is important to be able to reproduce them in experimental animals.

One strategy for creating these brain structural abnormalities early in development exploits neurotoxins that exert their effects by selectively killing cells that are multiplying. By administering neurotoxins during development, selective groups of neurons are eliminated in the brain.

Investigators used toxins of this sort to induce underdevelopment of the cerebral cortex, which produces enlarged ventricles, disrupts formation of the hippocampus, and reduces the size of the cerebellum. These studies revealed that the resulting abnormal synaptic circuitry of the brain reflects not only the deleted neurons, but abnormal connection patterns among the surviving neurons.

Underdevelopment of the cerebral cortex has been particularly associated with a relative overstimulation of this region by noradrenergic and dopaminergic neurons. These alterations may provide a link between the ventricular enlargement associated with the negative symptoms of schizophrenia and the overactivity of dopamine neurons thought to account for the psychotic symptoms of schizophrenia.

Excitotoxins are a group of compounds structurally related to glutamic acid, the major excitatory neurotransmitter in brain. Glutamate excites neurons by activating specific receptors linked to ion channels through which sodium and calcium flow when the receptors are activated. Current evidence points to at least three distinct receptor recognition sites for glutamate, which are named after their most potent agonists: kainic acid, quisqualic acid—both of which are found in the body naturally—and N-methyl-D-aspartic acid. Each of these receptors is linked to a distinctly different ion channel.

Overexciting neurons damage neural systems.

While glutamate receptors ordinarily mediate excitatory neurotransmission in brain, neuron degeneration occurs when they are excessively activated by their specific neurotoxin. Since the receptors for glutamate appear to be restricted to neurons and concentrated on their cell bodies, only neurons that have cell bodies near the injection site are affected.

Neuroscientists are only beginning to define the mechanisms involved in excitotoxin-induced neuronal degeneration. Recent studies point to an increase in intracellular calcium levels as an important factor. Calcium serves as a signal that activates a variety of enzymes, any of which can destroy a neuron. Researchers anticipate that particular pathways activated by calcium and leading to neuronal degeneration may vary, depending upon the neuronal type. Identifying these processes will lead to more incisive pharmacologic treatments for excitotoxin-mediated neuronal degeneration.

Since glutamate, the endogenous agonist for these excitatory receptors, is found in brain in remarkably high concentrations, it seems conceivable that it could cause neuronal degeneration if its release were excessive or its inactivation were insufficient. In the last 2 years, neuroscientists have found compelling evidence supporting this hypothesis. They have demonstrated that administration of antagonists for these receptors, especially the N-methyl-D-aspartic acid receptor, can prevent several types of neuronal degeneration that occur in animal models of neurodegenerative disorder. For example, administering an

antagonist for the N-methyl-D-aspartic acid receptor protects it against the neuronal degeneration that occurs in response to profound hypoglycemia.

The techniques of molecular biology will undoubtedly dovetail with neurotoxin research as they address the issue of selective neuronal vulnerability in psychiatric disorders. Huntington's disease provides a useful example. Excitotoxins are faithfully reproducing the pathology of this inherited disorder, and molecular biologic studies are closing in on the gene.

Several researchers have speculated that the defective gene responsible for Huntington's disease likely alters glutamate neurotransmission at the N-methyl-D-aspartic acid receptor. Cloning the gene should resolve the question within the next 5 years. If the hypothesis is true, a context for exploring the mechanism of neuronal death and strategies for pharmacologic treatment and prevention will become feasible.

Genetic factors may make some people more vulnerable to effects of toxins.

Similarly, molecular studies now suggest that genes in humans are responsible for certain forms of Alzheimer's disease. The genetic defects may result in the accumulation of abnormal proteins in neurons. Nevertheless, excitotoxin mechanisms could contribute to the selective neuronal vulnerability in cortex and hippocampus, since these neurons are enriched in N-methyl-D-aspartic acid receptors. Thus, neurons structurally compromised by the accumulated proteins could be rendered much more vulnerable to the cytotoxic effect of the neurotransmitter glutamate. Loss of hippocampal neurons enriched in N-methyl-D-aspartic acid receptors is consistent with this hypothesis. Thus, it may be possible to develop treatments that retard the progression of Alzheimer's disease even if the underlying molecular defect cannot be repaired.

In the years ahead, chemists will design neurotoxins to target an increasing array of neurotransmitter-defined neurons. At present, fewer than a half dozen specific neurotoxins are available, whereas the number of known neurotransmitters approaches 100. The bulk of these new neurotransmitters are neuropeptides, and their specific roles in brain function and behavior remain elusive. Site-directed neurotoxins could exploit metabolic specialization of specific peptide-using neurons or the expression of specific receptors that could be the target of neuropeptides. One strategy might exploit a potent toxin covalently linked to a peptide that would bind to the receptors selectively expressed by the neurons of interest.

Modeling the Nervous System

Scientists who try to construct intelligent thinking machines find themselves in awe of the computational achievements of the human brain. We do not understand human intelligence, and we cannot mimic it in artificial systems. Neuroscientists simply do not know how neurons

in the brain give rise to intelligence by their collective action. Neural modeling is an attempt to take what neuroscientists do know about the brain and use it to build models that simulate intelligent behavior as a way of furthering our understanding of ourselves.

Modeling is essential for comprehending how the brain computes, since when neurons are embedded in large networks, the whole becomes more than the sum of the parts. The ensemble behaves differently from what could be predicted by extrapolation from the behavior of single neurons or small circuits. These ensemble properties, which emerge only by combining many elements, are crucial for computation and behavior. The situation is very similar, in principle, to thermodynamics: the regularity of solids, the fluidity of liquids, and the expansiveness of gases could not be predicted by simple extrapolation from their component molecules.

Computer models reveal how groups of neurons work together.

Neural modeling is done by computer simulation. Neural modelers assume that all neurons are operating continuously and concurrently, aggregating signals that they receive from other neurons and intermittently generating impulses that travel down their axons and produce synaptic potentials. To approximate the signal processing capabilities of even a single neuron requires a large number of simple computing operations. Conventional computers, although they can perform only a single operation at a time, nevertheless can perform each operation very quickly. Thus it is possible to simulate the processing activity of a small network—about 100 units—in something like the time it would take the same processing to occur in the brain. However, with larger networks, simulation can be very slow, and often, some approximations are made, in part to speed the computation. Neural network modeling also draws heavily on mathematics. Several of the recent breakthroughs in the field are due to essentially mathematical insights.

Not long ago, a mathematician's only option when facing a complex system was to try to get approximate numerical solutions for the equations governing the system. This was often a very difficult task. Furthermore, even if it permitted prediction, it did not necessarily contribute to understanding; generalizations did not naturally emerge. Today, the mathematician strives to draw general conclusions about the types of states it can get in and how they can change into each other. Predicting the detailed behavior would be an Olympian feat, but it would not necessarily add to our understanding of how the system functions, just as predicting the pattern of 1's and 0's that will arise in a computer after many operations would not enlighten us about what the computer is accomplishing. The focus now is on qualitative properties of the ways in which nerves and neural circuits change with time, and on the long-term states into which these systems settle when left to themselves.

Researchers readily admit that analyzing neuronal models to capture the reality of the nervous system is on the frontier of mathematical

techniques. Nevertheless, it is safe to say that the effort will contribute substantially to understanding how the brain processes individual signals to produce behavior.

Neural modeling is progressing on the workings of individual neurons and of small collections of neurons. One of the most sophisticated individual neuron models emulates nerve impulse propagation down the axon. This analysis shows clearly that the isolated nerve axon can get into remarkable and unexpected states. For example, a neuron can undergo a sudden transformation from a steady to an oscillatory state, which occurs at a threshold current across the axonal membrane. The axon has a complex array of oscillatory states, which can emerge from each other under critical conditions.

Tiny changes can produce surprising results in nerve behavior.

Modeling has also shown that neurons probably have an inherent stability. When the forces acting on or within a nerve cell undergo slight changes, the long-term state that the neuron settles into eventually also changes, and usually the change in final state is small if the change in internal or external forces is small. Continuity of this kind is called "global stability." Sometimes, however, a tiny change in the internal or external forces causes a dramatic change in the final state of the system, or even in the number and types of final states. Discontinuity of this kind is called a bifurcation.

Finding that nerve cells can settle into two or more electrical states raises a possible problem: the nerve may settle into a state inappropriate for proper operation. If so, the result might be a malfunction in the brain producing a behavioral disorder. Thus, some mechanism must ensure that neurons settle into the proper state, and one model of small neural circuits has identified just such a mechanism. Nerve cells are presumed to always fire when they reach a threshold, and never fire if they do not reach that threshold. When the model's neurons acted in this fashion, the circuits settled into several different states. However, when the on-off nature of the nerve cell was adjusted to be partially random, so that nerve cells with excitatory input sometimes stayed off and those with inhibitory inputs sometimes turned on, the circuits made from these neurons eventually settled into one particular state. Thus, a neural model was able to show how what seems to be an undesirable property of neural activity—its randomness—can, in fact, have desirable consequences.

Nerve cells are a self-organized system, like weather and ecological systems.

Studies such as these depend on advances in an area of mathematics called nonlinear dynamics. This set of concepts and techniques explain how spatial patterns in complex systems evolve and change, such as clouds in weather systems, chemical reactions, embryos, and populations of animals and plants. These systems are said to be self-organizing, because their patterns grow and are shaped from within. Neuroscientists recognize now that the brain, too, is a self-organizing system and not a robot or reflex machine.

Chaos is an essential ingredient of self-organization; it is the basal state from which new forms of order emerge. Chaos is unpatterned and unpredictable activity that looks like random noise, and until recently was considered to be so. It is not. Researchers can generate this remarkable form of dynamic behavior by solving differential equations under conditions that were unknown 20 years ago but that are now fairly well understood.

One remarkable discovery, made about 3 years ago, is that electroencephalogram recordings can be described as chaotic, not noisy as has been assumed for 60 years. This means that brains may generate this activity in controlled, deterministic ways. These background waves, the little blips that appear in seemingly random fashion, are signals, not noises. Neuroscientists were mistaken in looking for signals in the noise, when the "noise" was really the signal.

Background blips are not noise but chaos in action.

Chaos has many forms, and each one has a degree of complexity that varies from the simple to the complicated, where complexity is described by a dimension, or what mathematicians call degrees of freedom. How many degrees of freedom do the different chaotic states have? How can neuroscientists measure them? How can they tell one kind from another? Theorists and experimentalists are vigorously attacking these questions.

One recent study used chaos and nonlinear dynamics to construct a model of the olfactory system that simulates the electroencephalogram signals recorded from an animal's olfactory nerves. This model consists of three different kinds of normal chaotic neural activity generated by the interactive neurons in the olfactory system. One kind is seen as a wave that carries information from one place to another in the brain's perceptual system for odor identification, like an electrical fluctuation that carries voices on a telephone wire. Another kind of chaos exists in the resting state between inhalations; it serves as a springboard for the odor identification that occurs with each inhalation. The third type of chaos occurs when a subject receives a novel odor that must be learned. Several research groups have now extended the study of these electroencephalogram patterns to the visual, auditory, somatic, and limbic systems in rats, rabbits, cats, monkeys, and humans. Major strides are now possible in the application of these new developments to the studies of human electroencephalograms.

As researchers refine these models and their predictions, they will begin investigating a new theory of behavioral disease. Instead of trying to find and fix a singular molecular error causing a given disorder, they will search for neural networks that have settled into an inappropriate steady state, becoming either more or less chaotic than normal. If found, researchers will begin to look for ways to perturb those circuits, forcing them out of the abnormal state and into the correct one. It is entirely possible that further study will show that conditions such as

Change in chaos may be a novel indicator of disease states.

psychoses, and behavioral fixations such as alcoholism, bulimia, and gambling, will turn out to have multiple molecular causes but only a few abnormal patterns. This could lead to a new family of therapeutic interventions.

In the next few years, modelers will conduct more elaborate mathematical analyses on realistic models of simple neurons and simple models of neural circuits. Large networks will not be the primary focus at this stage. Until the mathematical properties of neurons and small circuits are known, analyses of their behavior when aggregated into large arrays have no firm basis. It is tempting to work on highly stylized neurons arranged in highly stylized networks, but the whole point of the modeling effort proposed here is to capture the properties of the real brain, not an imaginary one that conforms to our preconceptions.

Before the end of the century, researchers will start modeling larger networks meshing small circuits of interlocking neurons. Since the number of neurons exceeds the number of brain-specific genes by five orders of magnitude, randomness and repetition must play an important role. Knowledge of the ground-plan of neural connections at a cellular level is still fragmentary, but it is growing fast, and substantial information will be available to the mathematical modeler by the time this stage is reached.

Some might say that neural network modeling should wait until neuroscientists answer all the other questions about the workings of individual or groups of neurons, arguing that modeling can only succeed when all the relevant facts are known. The history of science, however, demonstrates that research is driven by questions or predictions that arise from theory as often as it proceeds from accumulated observations and experimentation. Thus, attempts to discover how good our current understanding really is should turn to modeling to explore the adequacy of a set of principles postulated solely on the basis of experiment. When modeling reveals that the principles are inadequate, it will stimulate further research aimed at understanding the detailed basis of the discrepancy between theory and data.

Brain and Immunity

In recent years, neuroscientists have begun to study the mechanisms by which the nervous system translates psychological factors into physiological states that can affect physical health. In particular, a growing group of researchers are working to understand how the brain influences, and is influenced by, the various systems that defend and repair the body's tissues. This field, called psychoneuroimmunology, will contribute greatly to our understanding of two central systems in the body.

The keystone of the immune system is the thymus gland, in which various immune cells differentiate. Besides its specific immune functions, the thymus is also an endocrine gland that secretes hormones that affect other tissues, including the brain. Indeed, as the first endocrine gland to become functional during development, the thymus gland is now thought to affect brain development, both early and later in the transition to adolescence. The thymus actually triggers adolescence by sending chemical signals to the brain region called the hypothalamus, which in turn stimulates the gonads. However, the thymus receives neural inputs from the brain and spinal cord, which probably affect its glandular as well as its immune functions. Further knowledge about the development of brain-thymus interactions will therefore shed light on how the brain may affect its own development.

Immune system and brain both survey the outside world.

The immune system also functions as a sensory adjunct of the nervous system, because immune cells called lymphocytes have receptors that recognize foreign molecules, called antigens. Learning about the antigen receptors on lymphocytes may help us understand more about the chemical receptors used by the smell and taste senses, as well as the chemical receptors on nerve cells that bind neurotransmitters.

One important recent finding about the brain is that, contrary to what most scientists had thought, the brain is not immunologically inert. Several studies have now shown that a particular type of glia cell, the microglia, are actually immune cells resembling macrophages in the rest of the body. Whether they are identical or only similar in origin and properties to the macrophages of the immune system is still controversial. Their function is a mystery, as they are joined by macrophages from the immune system during brain infection or injury.

Brain's internal immune system may affect behavior.

Since immune system macrophages secrete at least 60 active substances that affect other cells, microglia may also secrete substances that play important roles in the modulation of brain function. Researchers are now working to detect and isolate such substances, which would open yet another door on brain regulatory mechanisms.

The more scientists learn about the brain and immune systems, the more the two systems seem to have in common. For example, lymphocytes and brain cells share a certain antigen, called Thy-1. Thy-1 appears to be an attachment point for viruses that attack both immune cells and brain cells.

As further study uncovers more information on why brain cells and immune cells share common properties such as surface antigens and receptors for neurotransmitters, other functional analogies between the nervous and immune systems will be illuminated: for example, their common need to deal with unfamiliar environmental stimuli and possession of appropriate memories.

Recent experiments have shown that the immune system initiates at least some neurally mediated behaviors that are adaptive when an

individual has an infection. For example, certain immune cells release a hormone called interleukin-1. In the immune system, interleukin-1 causes some immune cells to release interferon, which blocks viral replication, and causes other immune cells to release forms of oxygen that destroy bacteria. However, in the brain, interleukin-1 produces three responses: fever, which helps to kill microbes by thermal destruction; thirst, leading the individual to replace the needed water lost by fever-induced perspiration; and sleepiness, leading the individual to rest and dreamless sleep, during which healing and recovery occur. Other immune factors may also affect brain function in behavior, and finding them could open new therapeutic regimens for a variety of illnesses.

Links between brain and immune system may offer new therapies for mental illnesses.

Much of the work in the next few years will focus on discovering the chemical and neural connections that link the immune and nervous systems. With this information, researchers will be able to find the genes involved in these processes and study their regulation. In addition, investigators will begin exploring the therapeutic uses of these chemical factors, both in infection and mental health applications.

As part of this effort, neuroscientists will discover the full complement of neurotransmitter and hormone receptors on immune tissues and cells. They will learn about the specific functional roles of these and the other receptors that have already been reported on immune tissues and on regulatory, accessory, and effector cells.

Future experiments will also elucidate the ways in which the neural and chemical links between the hypothalamus and thymus glands control behavior and immunity. Already, researchers have discovered a number of peptide hormones produced by the thymus that bind to receptors in the hypothalamus. Considering the important role that the hypothalamus plays in controlling behavior, finding these peptides will have a major impact on learning how the immune system also controls behavior.

As scientifically and medically important as these studies are by themselves, they are part of a larger field that could be called the psychobiology of defense and repair. An organism attempts to maintain homeostasis despite the ever-present burden of inherited and acquired biochemical defects. Therefore, an organism's state of health reflects in part the varying success of all of the defense and repair systems in preventing and correcting further damage to its structural, functional, and, above all, informational molecules. Understanding how the mind, via the nervous system, affects all of the systems that defend or repair biomolecules and the cells and tissues they constitute would obviously permit enormous advances in health care.

The information in the DNA of a fertilized ovum is there to specify not only its development into a new organism but also the subsequent moment-to-moment biochemistry in every eventual cell of that organism during its lifetime. When oxygen-free radicals, produced by various

chemicals and as part of everyday metabolism, evade antioxidant defenses and damage DNA bases and strands, a DNA repair system is evoked. In humans, it comprises at least 15 enzymes, which, after breaking the DNA chain to which an oxidant-damaged nucleotide is attached, remove the damaged nucleotide and hundreds of surrounding nucleotides. Then the missing section of DNA chain is resynthesized from one end of the break, using the complementary chain as a template for the insertion of replacement nucleotides, until the remaining nick is ligated. Because nature is noisy, incorrect nucleotides are inserted at a low but real rate, causing somatic mutations that are perpetuated in each succeeding round of cell division. Most mutations are deleterious. Thus the DNA repair system is intrinsically mutagenic and carcinogenic. However, it presumably causes far fewer mutations than would unrepaired DNA damage, for even small declines from its normal level of activity may have serious physiological consequences.

According to recent reports, stress causes DNA damage, which consequently evokes an increase in DNA repair. In experiments with rats, researchers found that a variety of stressful situations significantly increased the number of sister chromatid exchanges, an indicator of chromosome damage, in proportion to the severity of the stress. DNA repair subsequently increased. These animals also produced extra amounts of adrenocorticotropin and beta-endorphin, which other studies have shown can affect the activity of macrophages and neutrophils (members of the family of immune system cells called phagocytes). Phagocytes release oxygen-free radicals in order to destroy alien entities and debris. There is always some damage to surrounding healthy self-cells, so stress may damage DNA in this way by means of oxidizing radicals.

Psychological stress may cause damage to DNA.

The mechanisms of stress effects on DNA repair are unknown, but neuroscientists hope to remedy this knowledge deficit within the next decade. DNA repair can be inhibited by a number of pharmacological agents, some of which may mimic endogenous inhibitors affected by or consisting of neurotransmitters and hormones; insulin, for example, delays DNA repair. All genes, including those that dictate the biosynthesis of DNA repair enzymes, neurotransmitters, and all of the estimated 90,000 other specific gene products in the cells of a human body, are ultimately regulated by signals derived from the environment, expressed as neurotransmitters and hormones. Since some of these signal molecules represent emotions, it makes sense to look for emotional effects on the biochemical constituents of all defense and repair systems.

Genes and Behavior

One approach to the study of behavior assumes that most, if not all, behaviors have some genetic underpinning. Either classical genetic methods or recombinant DNA techniques are used to probe and understand the molecular basis of behavior.

Clarifying genetic determinants of behavior.

In classical genetics, researchers identify natural variants from wild or, alternatively, lab strains that show aberrant, unusual, or distinguishable behavioral features. They then mate these different strains and attempt to find out whether a particular behavior is passed to future generations in a predictable pattern of inheritance indicating that a single gene underlies the difference or, in a more complex fashion, indicating that two or more genes underlie the behavioral difference.

Consider for a moment a behavioral abnormality that evidence suggests is due to a single mutation at a particular genetic locus. Good examples are mutants of the fruit fly with learning deficits. These single gene mutations cause a fly to fail to learn or to learn extremely poorly. When a population of flies is subjected to a learning regime, normal flies will learn to avoid a certain odor and, in doing so, move from location A to location B. Flies that fail to learn are much more prevalent in location A, and these individuals can be collected and bred. If their failure to learn is indeed due to a mutation that interrupts learning, these individuals give rise to a new mutant population, all members of which will fail to learn or learn much more poorly relative to the initial wild type population. Researchers then assume that the mutant strain is missing a gene product necessary for normal learning. Indeed, this is one of the few foolproof ways of identifying genes and gene products important for brain development and function. Using this approach, researchers have succeeded in finding genes necessary for learning, visual responses, circadian rhythm behavior, and ion channels.

Single genes can dramatically affect behavior.

With recombinant DNA technology, the investigator can deliberately introduce variant or mutant sequences of DNA into the animal. In general terms, a known piece of DNA, coding for a known protein, function, or variant that the investigator suspects has behavioral consequences, is introduced into the germline of the animal and therefore becomes a stable and inherited feature of the newly created strain. Researchers can then determine to what extent the behavior of this strain was changed or altered in response to the addition of this variant gene.

The learning paradigm used with the fruit fly has given rise to a series of mutants whose genes appear to code for components of the signal transduction pathway. The classic example here is the original learning mutant, called dunce. Cloning of the dunce gene showed that it codes for a known and well-studied enzyme in mammalian systems that plays a key role in triggering nerve signals. This example, coupled with a number of more indirect but similar experimental approaches, places the signal transduction pathway as a key and important player in learning.

Another example of mutants that researchers have analyzed are period mutants of the fruit fly. Flies that are missing the period gene have no biological rhythms but are otherwise quite normal. This indicates that this gene is unnecessary for normal viability and must thus represent some higher order function required for the manifestation of biological

rhythms and perhaps for other subtle, as yet undescribed behaviors. Investigators have cloned and identified this gene, and have found that the protein coded for by this gene manifests weak similarity to an unusual class of proteins called proteoglycans.

Recent experiments have demonstrated that a number of fruit fly mutants, originally identified on the basis of unusual behaviors, such as shaking or paralysis at high temperature, have abnormal ion channel genes. Although these studies are in their infancy, this identification appears solid because the cloned genes corresponding to these mutants have very strong primary sequence homology to known vertebrate ion channel components. Manipulating these genes is very likely to provide real insight into the way these various ion channel components contribute to normal behavior in humans.

Neuroscientists anticipate that recent technological advances, specifically the cloning and sequencing of genes and the ability to reintroduce these genes into the germline of animals, will produce a large number of new and exciting discoveries. Researchers will clone more genes of behavioral significance, for example, as they develop novel biological assays with which to identify behavioral mutants.

Genetics of lower organisms has direct application to human biochemistry and disease.

In addition, identifying new fruit fly genes, even of ·unknown biochemical function, will enable researchers to identify homologous mammalian genes through their use of gene probes and monoclonal antibodies. These reagents can be applied not only to the species from which the gene was cloned, but across species barriers, often to great advantage. With these reagents, investigators can hope to identify and isolate the mouse or human gene that is the equivalent or close relative of the fly gene, and then identify the locations in the mammalian brain where these gene products reside. Approaches such as these will lead to hypotheses concerning the anatomical locations of specific mammalian behaviors.

Indeed, this approach will work in the human-to-fly direction as well, and may lead to profound discoveries. A large number of mammalian genes are suspected to have behavioral importance—their products are found in high concentrations in the brain or central nervous system—but these suspicions cannot be tested with current methods. One route that neuroscientists will exploit is to use these mammalian genes to isolate the homologous fly genes. Over the last couple of years, in fact, research laboratories worldwide have used this method successfully to isolate and clone a significant number of fruit fly genes, identified initially on the basis of their homologies with known mammalian genes. With the genetic tools available in flies, researchers can generate mutant genes, insert them into flies, and examine the resulting mutant animals for behavioral anomalies.

Further into the future, molecular biologists will perfect methods, now feasible only in simple organisms such as bacteria and yeast, to allow directed integration of recombinant DNA in animals. A technique of this

kind, applicable in both vertebrates and invertebrates, will allow a piece of cloned DNA to act as a specific bullet with which an investigator can disrupt specific genes. With directed integration of DNA, researchers will be able to knock out specific genes at will and examine directly and swiftly the behavioral consequences of such gene disruptions. In this way, neuroscientists will be able to build on studies underway today to make dramatic progress in understanding the genetic basis of behavior.

Neurobiology of Time

Circadian rhythms are built into nearly every living creature.

Living organisms possess internal biological clocks that control the timing of different biological processes. Humans isolated without exposure to day and night or other time cues continue their normal sleep/wake cycles for weeks. The significant fact, however, is that the day length for isolated persons is approximately 25 hours, indicating that they have an internal clock modifiable by external cues. Scientists refer to these rhythms as circadian, meaning about (circa) one day (dies). Microorganisms kept in the laboratory under rigorously uniform conditions behave in the same way, suggesting that their clocks are similar.

The clock controls many aspects of an organism, well beyond the many different processes associated with activity and rest. Conversely, many things may affect or control the clock, most obviously and importantly the light that impinges on us every day and the darkness that envelops us at night. The study of these two aspects—the way in which the clock controls the cell and the organism, and the effect of external conditions on the clock—will provide important insights into the basic timing mechanism and its action in the human.

Finding the brain's timekeeper.

Researchers are making progress in several areas. One involves the discovery of brain centers that are involved in clock function. In mammals, studies have demonstrated that the suprachiasmatic nucleus has an important controlling or coordinating role, which provides an important clue to the structural organization and nature of the system. The relationship of this center to visual pathways is especially significant. Other studies have shown that the metabolic activity of this part of the brain is strongly circadian, with large day-night differences.

Recent experiments have discovered that the metabolic activity and spontaneous electrical activity of the suprachiasmatic nucleus oscillates with its own intrinsic circadian rhythm. This rhythmic activity persists in animals even after severing connections to other parts of the brain, as well as in isolated brain slice preparations of the suprachiasmatic nucleus. These findings suggest that the suprachiasmatic nucleus contains self-sustained circadian oscillators. Other studies have shown that neural transplants containing suprachiasmatic nucleus tissue are capable of restoring circadian behavioral rhythms in animals in which this part of the brain was destroyed.

Although the general organization of the mammalian circadian system is becoming clearer, the intrinsic anatomy of the suprachiasmatic nucleus, its incoming and outgoing projections, and the neurochemistry of the cells are only beginning to be understood. In addition, little information is available on non-suprachiasmatic nucleus components of the mammalian circadian system. The neurotransmitters mediating the various inputs and outputs are also largely unknown, and determining what they are is particularly demanding because more than 20 neurotransmitter-like substances have been found in the suprachiasmatic nucleus region.

In nonmammalian vertebrates, the pineal gland and the eyes play a major role in regulating circadian rhythms. In birds, it appears that the suprachiasmatic nucleus, the pineal, and the eyes are all involved in circadian behavior, although species differ significantly in the relative contribution of each of these structures. The pineal gland plays a dominant role and acts as a circadian pacemaker driving behavioral rhythms in sparrows. The suprachiasmatic nucleus, however, is still necessary for normal circadian behavior. In quail and pigeons, the eyes also contribute to circadian behavior. Researchers have found a similar pattern of organization in reptiles in which all three structures are involved. The eyes and the pineal have also been implicated in circadian organization in amphibians and fish. Although neuroscientists' understanding of the physiological organization of vertebrate circadian systems is only beginning, this information from other species is of fundamental importance to elucidating the evolution, development, and function of vertebrate nervous systems.

Circadian clock is controlled by genes and proteins.

Experiments have produced fruit fly mutants with altered circadian clocks: some mutant clocks run fast, some run slow, and some appear not to keep time at all. The next step, now underway in several laboratories, is first to isolate and characterize the genes responsible and then to find out what is altered in those mutants. This will give researchers important insights into the cellular chemical components of the clock.

In unicellular organisms the entire clock and all the hands of the clock are necessarily confined to the single cell. In the bioluminescent microorganism Gonyaulax, light emission is brilliant by night and dim by day. Biochemically, luminescence involves several factors, including an enzyme called luciferase. Recent research has shown that this enzyme actually appears and disappears each day: it is present at night but absent in the daytime. This has provided one of the first—and very important—clues concerning how the clock controls the cell: by synthesis and destruction of essential biochemicals.

Scientists recently discovered that this process involves a pulse of synthesis at one time of day, and that this synthesis is controlled at the level of the protein synthetic system—the ribosomes—and not at the level of DNA and RNA. It is significant and interesting in this connection that drugs that have an influence on the clock are the same ones that act by inhibiting protein synthesis in higher organisms.

Another model system that scientists have studied with some success in recent years is a certain sea snail, which has a circadian clock built into each eye. When the eye of the sea snail Aplysia is dissected together with its optic nerve, these cells survive as a piece of organized tissue for up to 2 weeks. Moreover, the circadian clock in this isolated eye continues to function over this 2-week interval. The clock can be read by recording the number of nerve impulses per time interval that are conducted along the optic nerve. Studies with this system have found that the circadian process is controlled at the level of DNA transcription rather than protein synthesis; perhaps more than one mechanism controls circadian processes.

From such experiments, researchers will uncover how various cellular processes affect and are affected by the biological clock. Are compounds that are known to control cellular process, such as calcium or various neurotransmitters, involved in any cases? Is protein modification, now known to be of key importance in regulating cellular growth and cell malignancy, involved? Some evidence in some systems favors each of these possibilities, and further research will answer these questions.

Scientists are now beginning to apply new techniques that allow them to separate about 1,000 proteins simultaneously on a two-dimensional surface. The pattern of these proteins can be compared at many different times during a circadian cycle. Since both protein synthesis and DNA transcription depend on specific proteins being synthesized, one can directly evaluate what is occurring. A few laboratories are taking this approach, but the work is very demanding and time consuming. Nevertheless, this method will play an increasingly important role in chronobiology research.

Once a circadian set of proteins are recognized, researchers will be able to prepare DNA probes to search for the genes that code for the proteins. They will then be able to study the expression of these genes to determine the relative role that protein synthesis and genetic expression play in controlling the circadian clock.

A second step that researchers will take in the near future involves studying isolated circadian neurons. The major question is whether a single isolated circadian neuron exhibits circadian oscillation. It should be possible to test this with a variety of approaches. One technique uses fluorescent probes in intact cells to measure the concentration of simple but important ions such as calcium, potassium, and hydrogen as well as the voltage difference across a cell's membrane. Such probes are being developed by a number of investigators in cell biology and are among the most exciting developments in this decade.

Before the next century, we expect the genes controlling circadian oscillations in several different systems to be cloned. The next step will be to attempt to induce the circadian function in cells that normally do not contain this function. The most likely cell for this experiment is the

toad egg cell, a current favorite among researchers because it is so large, allowing intracellular injection with ease. In addition, this cell has faithfully translated many foreign messenger RNAs that have been injected into it.

Researchers will also begin using the technique of attaching miniature electrodes to the outside membrane of isolated circadian neurons in cell culture. This procedure will allow scientists to observe how a single ion channel behaves over periods as long as an hour by recording electrical signals whose magnitude is on the order of a few picoamperes. This technique will probably never record the behavior of a single ion channel over an entire circadian cycle, but it should be possible by statistical evaluation of many hourly records to decide what ion channels are actually modulated during such a cycle.

Other experiments will attempt to discover what external factors influence biological clocks. Light, for example, has a pervasive and profound effect on clocks. It sets and resets the clock each day, and the clock may run faster or slower depending upon the brightness or color of the light. Higher organisms and humans have eyes or special photoreceptors with neuronal pathways to the brain. In fact, the eye is actually part of the brain, and the close relationship between the visual pathways and the clock center in the brain signals an important involvement of light in the clock.

Unicellular organisms have no eyes, but their clocks are exquisitely sensitive to light in the same general way as are higher organisms. Different colors of light are known to affect the clock in different ways, and in higher organisms this color effect does not always coincide with that for vision. Studying the action of light in unicellular organisms will prove to be a powerful way to dissect and analyze an important component of the clock without the complications of vision.

In addition to basic knowledge about the nature of the clock itself, such studies can be expected to lead to the development of therapeutic drugs for chronobiologically related diseases, including mental health problems such as depression and insomnia. Scientists have isolated a substance from higher organisms which, when added to the culture medium, affects the period of the rhythm in Gonyaulax. Some disorders in humans may relate to internal clocks that run too slow or too fast, and a compound of this type might have therapeutic value.

Lithium may control mania by resetting the circadian clock.

Interestingly, the drug lithium increases the period of the circadian oscillator in a dose-dependent way. It can be assumed that in humans the period-lengthening effect of lithium on the circadian oscillators plays an important role in stabilizing the manic-depressive patient, although how this is brought about is far from clear. Within the next decade, neuroscientists will succeed in understanding the anatomy and functional organization of circadian systems.

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NIMH INITIATIVES IN THE NEUROSCIENCES

Introduction

The National Advisory Mental Health Council (NAMHC) of NIMH concurs with Congress that the fields of clinical and basic neuroscience research are poised for major breakthroughs in understanding the brain and brain/behavior relationships. The new knowledge within our grasp will profoundly affect our future concepts, treatment, and prevention of mental illnesses. A major investment in neuroscience research is needed now if we are to realize this potential.

NAMHC has found that the highest research payoffs are realized through individual investigator-initiated grants. Yet, in the past 2 years, NIMH has been unable to award grants to a great many scientists whose peers assigned high-priority scores to their applications. NAMHC therefore recommends that Congress significantly increase appropriations for investigator-initiated grants in neuroscience research to approximately $54 million. This will contribute to the support of these high-priority research grants and allow NIMH to mount new initiatives in those research areas that promise to achieve the numerous breakthroughs outlined in this report. Requests for Applications (RFAs) are anticipated in the following areas: Molecular Neurobiology, Nonlinear Dynamics, Virology, Immunology, Neural Networks, Developmental Neurobiology (growth factors, target proteins), Neuroplasticity/Transplantations, Neurotoxins, Computer Modeling (drugs, receptors, proteins), Behavioral Neurogenetics, Chronobiology, Impact of Brain Mechanisms on Development and Course of Illnesses, Behavioral Manifestations of Neurological Disorders, Neurobiology of AIDS, Receptor Regulation/Dynamics, Cotransmission/Neuropeptides, Neuroethology/Ethopharmacology, Transduction Mechanisms, Imaging Development, Functional Neural Circuits, and Neuroscience Workgroups.

The neuroscience initiatives planned for both the extramural and intramural research programs are described below. The NAMHC has provided an overview of each initiative, followed by its explicit recommendations and estimates of the required resources.

EXTRAMURAL RESEARCH PROGRAM

Molecular Neurobiology Program

The rapid development of methodology in molecular biology over the past decade has produced increasingly powerful research tools. Their application to mental health and mental illness should generate significant findings in at least three major areas: (1) the use of

recombinant DNA probes to analyze and understand neurotransmitter systems in the human brain, (2) the use of genetic engineering methods to develop biologically active molecules for treating psychiatric illness, and (3) the use of recombinant DNA probes to analyze inheritance patterns of mental illness in families.

During the past 5 years, the neurobiology program of the Neurosciences Research Branch (NRB) has encouraged molecular biologists and molecular neurobiologists to apply their expertise to problems relevant to the mission of NIMH. NRB has organized a major workshop on molecular neurobiology, bringing together some of the world's foremost authorities in molecular neurobiology, neuroscience, and psychiatry research. This comprehensive review will help determine policy and priorities for molecular neurobiology research at NIMH.

The NAMHC recommends that NIMH, in order to further stimulate research in molecular neurobiology, should:

- create a **Molecular Neurobiology Program** within the Neuroscience Research Branch charged with developing this area of research;

- establish **Centers of Excellence in Molecular Neurobiology and Mental Health**; two such centers should be funded each year at an estimated cost of $3.0 million per center per year;

- foster communication and spontaneous collaboration among relevant scientists through conferences, symposia, etc.

Computer Applications in Neuroscience Program (CANS)

Computers are rapidly becoming essential tools in several aspects of neuroscience research. Among their many applications are (1) management of information, (2) analysis of experimental data including statistics, (3) modeling of neural systems, (4) three-dimensional modeling of drug and receptor molecules and interactions, (5) imaging of brain function and pathology, (6) application of mathematical and physical science principles to brain function, e.g., nonlinear dynamics, (7) control of experimental equipment, and (8) scientific communication.

In some areas, significant progress has already been made, e.g., computer-assisted drug design and receptor modeling. In other areas, the problem exceeds the ability or capacity of individual laboratories. NRB has organized or plans workshops to further enhance and develop the field and stimulate grant applications. For example, NRB is sponsoring a series of workshops on the application of nonlinear dynamic theory to neuroscience and is currently organizing a workshop on computer-assisted drug design.

Greater integration of computers in neuroscience will open new avenues

of investigation. For example, researchers will be able to simultaneously record the activity of individual nerve cells from several areas of the brain in a behaving animal, a feat that is nearly impossible today in terms of data collection and that defies current analytic techniques. Among the many usages that can be envisioned are (a) new ways of visualizing and conceptualizing brain functions, (b) improved diagnostic capability of brain imaging techniques, (c) acquisition of data in a format compatible with existing data and readily shared with collaborators, (d) reduced time and effort to maintain awareness of the neuroscience literature, (e) more effective indoctrination of non-neuroscientists into the current state of research, and (f) more rapid and formalized teaching of students.

The NAMHC recommends that NIMH:

- establish a **Computer Applications in Neuroscience Program** in the Neurosciences Research Branch;

- indicate to the field a serious commitment to and long-term investment in CANS through the allocation of staff and funds for the support of research and training, organization of workshops and conferences, issuing RFAs, and significant coordination and leadership;

- explore new uses for computers in the exchange of neuroscience information by establishing a **Neuroscience Bulletin Board/ Technology Information Data Base**.

A minimum of $1 million per year for the support of investigator-initiated research projects is required. In addition, $500,000 in contract funds is required to develop software for neuroscience application. Support for a neuroscience bulletin board and experiments in scientific communication initiatives are estimated to cost $250,000 per year.

National Neural Circuitry Data Base

A recent report from the National Academy of Sciences "Models for Biomedical Research: A New Perspective" states, "We seem to be at a point in the history of biology where new generalizations and higher order biological laws are being approached, but may be obscured by the simple mass of data."

Our current understanding of neuroscience is rooted in complex relationships involving enormous amounts of data. These data have been obtained from experiments and observations over the entire domain of neuroscience. The explosion of information on the number of neurotransmitters, neuromodulators, receptors, and ion channels and the development of methods that permit sensitive detection of neurochemicals in the brain have contributed to this information overload.

Few scientists are capable of keeping up with this ever-increasing wealth of information, let alone searching it for new or unsuspected links and important analogies. Fewer still are able to grasp the whole, i.e., see the "forest for the trees," and thus come to a greater understanding of how the brain acts in human behavior. Yet this is necessary if the continued exponential generation of such data is to lead to major conceptual and medical breakthroughs.

Current computer technology would allow the creation of a **National Neural Circuitry Data Base** that would enable neuroscientists to input data from an experiment as they are generated and compare them with what is currently known about the system being studied—numerically, textually, and graphically.

Several important, specific benefits are anticipated from the development of a neuronal circuitry data base, including: integration of a broad range of information in the design of experiments and the development of new theories; aid in identifying misconceptions based on an incomplete data base; increased dissemination of information to the neuroscientific community as a whole; increased availability of current information to clinicians and educators; and a broadened range of neuroscientific thought to encompass the whole and not just the parts.

On a practical level, a data base would speed the progress of science now delayed by information gathering, and increase the sharing of cutting edge data among laboratories.

The NAMHC recommends that NIMH:

- be the lead agency in a cooperative agreement with other Federal agencies and investigators in the field to develop a **National Neural Circuitry Data Base**. Over a 5-year period this would cost an estimated $5.0 million.

Neuroscience Workgroups in Mental Health

A growing number of specialized fields and the new technologies used in these fields are being brought to bear in basic biomedical research generally, and quite dramatically in basic neuroscience research. The continuous, rapid cycling of specialization, innovation, application, and generalization has become the hallmark of modern science. This mode of endeavor will dramatically alter the pace and interactions of theoretical development, research experimentation, and practical application. If the field of mental health is to benefit from the advances brought by this new synergism, there must be a mechanism that encourages the application of new fields of study and new technologies to mental health research problems—a mechanism that allows the continuous integration and cross-fertilization of new ideas and techniques from multiple disciplines to generate novel scientific opportunities.

The support of **Neuroscience Workgroups** is proposed to provide a unifying framework within which diverse research disciplines and approaches may be productively combined to address focused and well-defined questions that are on the frontier of basic research in mental health. A Neuroscience Workgroup should be characterized by an urgent, well-defined research question, novel approaches to the question posed, nonduplication of ongoing work, advanced technologies and leading researchers, with cross-fertilization enhanced by unique working relationships without restriction to geographical and/or departmental boundaries.

A single Workgroup is currently being funded on a pilot basis at New York University in collaboration with researchers at Yale University and at the Karolinska Institute in Stockholm, Sweden. This workgroup is pursuing the complex of questions related to the colocalization of diverse transmitter substances in single neurons within the central nervous system.

The Workgroup approach is expected to accelerate the development of new hypotheses and research findings, thus moving the field of basic mental health research to a new plateau. Laboratories now exist throughout the country that deal with specialized areas within the basic sciences. These laboratories and the areas of specialization are increasing annually. Encouraging the collaboration of such labs on issues of special importance to mental health is expected to stimulate research in areas not yet being studied, spawn opportunities for cross-fertilization among disciplines, and generate new insights throughout the field.

The NAMHC recommends that NIMH:

- establish two or three new **Neuroscience Workgroups** each fiscal year;
- evaluate this program in 5 years with the goal of recommending the maximum number of Workgroups considered to be beneficial for attaining the goals described above.

The Neuroscience Workgroup Program should be funded through the program project grant mechanism. The annual cost of a Workgroup should range between $500,000 and $2 million.

Centers for Neuroscience in Mental Illness

NIMH has determined the need for new research approaches to the problems of mental illness. The technologies of neuroscience and allied disciplines offer new insights into the research problems related to mental disorders, and should improve our understanding of the clinical symptoms, pathophysiology, etiology, and treatment of these disorders.

For some years, clinical research has generated hypotheses implicating genetic, viral, developmental, neurochemical, and other biological factors in mental illness. Basic science research is now at the point of being able to extend these hypotheses as well as to generate new hypotheses. The scientific opportunities offered by the integration of basic and clinical approaches appear to hold great promise for mental illness, but a new research framework is needed to pursue comprehensive, yet integrated, research on specific diagnostic categories. Thus, the Institute proposes a program of **Centers for Neuroscience in Mental Illness**, each Center to be devoted to the examination of a specific disorder; for example, there might be a concerted effort on depression or anxiety disorders. Individual centers are to be established only when collaboration between basic and clinical approaches becomes opportune and real.

A program announcement introducing this concept for schizophrenic disorders was issued in the Spring of 1987. It is expected that one or two Centers in this research area will be funded in FY 88.

Cooperative relationships between departments/institutions with outstanding clinical resources and departments/institutions with the most advanced basic science resources is seen as a next step in our efforts to solve the nation's mental illness problems. The intellectual interaction between clinical and basic researchers as well as the sharing of advanced approaches, technical resources, subjects, and data will advance the rate of progress in understanding mental illnesses that are increasingly seen as having a biological basis.

The NAMHC recommends that NIMH:

- fund a minimum of two Centers in each fiscal year devoted to a specific mental illness, as appropriate.

Each Center will be funded for a minimum of 5 years: the estimated initial costs are $3 million a year for each Center.

Natural Products Screening Program

Some of our most valuable therapeutic drugs have been isolated from plant and animal sources. These include reserpine (the first antipsychotic), morphine, numerous antibiotics (such as penicillin), digitalis, and a number of anticancer agents.

Despite the advances made in the last three decades in utilizing chemical synthetic approaches to drug design and in sophisticated structure-activity studies, a primary need still exists for the discovery of new therapeutic agents. Although literally thousands of chemicals have been synthesized and tested, numerous gaps remain in the therapeutic armamentarium for psychotropic drugs. In the early 1900s, many pharmaceutical firms and academic investigators were involved in collecting and screening natural products for biological

activity. In recent years, these investigations have been largely curtailed. For example, pharmacognosy, the study of drug-containing plants, has largely disappeared as an academic discipline. The most important of the many reasons for the decline in this type of research included low rates of payoff and high costs.

Recently, however, a number of developments have made the search for naturally occurring drugs an important research pursuit. The first compelling reason is the rapid disappearance of the flora and fauna of tropical climates, particularly in the tropical rain forests. If these natural sources of potential chemicals are not explored now, they may be lost forever. The second reason is that the National Cancer Institute (NCI) has launched a comprehensive program to collect and screen samples of plants and animals for anticancer activity. Constructive discussion with NCI has begun in order to effect a mutually beneficial use of these resources, currently involving a commitment of $8 million by NCI. Private botanical museums or private investigators interested in this type of drug discovery process could also be recruited. In addition, large numbers of plant and animal samples have undoubtedly been collected already that could be tested, now that the cost per sample has been greatly reduced. The third reason, and perhaps the most germane, is the new knowledge base in the neurosciences and the availability of rapid, appropriate in vitro test systems for the rapid screening and evaluation of potential psychoactive agents.

The NAMHC recommends that NIMH:

- cooperate with NCI to obtain representative samples that are being collected under their natural products collection program;

- formulate specific plans for a natural products screening program to be implemented through a series of contracts.

The cost of implementing a modest drug screening program would require about $4.0 million per year. The exact costs would depend on the degree of cost-sharing by other institutions and by whatever financial incentives can be provided to private sector firms interested in drug development.

Brain Bank Program

The ultimate definition of any human disorder will come from testing hypotheses in the human population. For psychiatric illnesses, this will require the establishment of a registry of well-diagnosed psychiatric patients willing to donate their brains to psychiatric research upon death, as well as the establishment of regional brain banks to collect and distribute the human postmortem brain tissue samples.

The NIMH Neurosciences Research Branch, in conjunction with the National Institute of Neurological and Communicative Disorders and Stroke, currently supports two human brain tissue resource centers. These facilities have served as a resource to the neuroscience

community for approximately a quarter of a century. Today, they are unable to meet the current demand of the research community for well-diagnosed brain tissue samples.

The NAMHC recommends that NIMH:

- establish a mechanism for prospective case finding, diagnosis, and creation of a centralized registry of voluntarily preregistered, prediagnosed tissue donors through the contract mechanism;

- when individuals die, have the tissues accessed by regional brain banks and distributed for further neuropathological and neurochemical research.

Using the contract mechanism, $5 million will be needed to establish a registry of patients consenting to donate their brains and to support five regional brain banks for the ultimate collection and distribution of brain tissue for neuropathological and neurochemical examination.

Tissue Bank Program

One of the fundamental goals of neuroscience research into mental disorders is to discover the primary causes of these diseases and thereby develop methods for their cure and prevention. One major promising approach is discerning the genetic factors that predispose to these illnesses. There are now markers for approximately 50 percent of the human genome, permitting highly sophisticated and comprehensive linkage studies. No one knows whether single gene disorders exist in psychiatry, but medical disorders that were once thought to be multifactorial turned out to have single gene components.

The identification of a linkage marker for a major mental disorder is one of the most promising scientific opportunities in psychiatry today. At the same time, it poses a serious logistic dilemma to interested researchers, namely, no single laboratory is capable of obtaining enough properly characterized biological material to carry out such studies. This circumstance virtually demands that NIMH assume a leadership role in the field. By the development and subsequent maintenance of a Tissue Bank Program, the Institute will be performing an invaluable service to both the research community and its major constituents— psychiatric patients and their families.

The NAMHC recommends that NIMH:

- establish a cell storage center for the study of the genetic linkage in schizophrenia, manic-depressive disorder, Alzheimer's disease, and other psychiatric disorders;

- recruit patients with these disorders and members of their families and collect diagnostic and behavioral characteristics on these subjects through structured interviews.

This project will provide investigators with extensive clinical and biological material for an incisive advance in the genetic transmission of serious mental illness. The cost over the first 3 years of this program is estimated at $3 million. In subsequent years, the cost of maintaining the facility and providing tissue samples and data to interested investigators is expected to total $1 million per year.

Instrumentation Resources

Instrumentation lies at the very heart of advances in the field of neuroscience. The increased complexity in neuroscience research depends on sophisticated methodology and expensive equipment and instrumentation. The growth of equipment needs has exceeded the availability of research funds for instrumentation in the mental health field. For the past 9 years, NIMH has invested only 2 percent of research grant funds for equipment.

A critical issue is that equipment purchases allowed on present research grants do not provide for general upgrading and new laboratory instrumentation. Given the explosion of new technologies, most equipment becomes outdated within 5 years. Even standard equipment usually needs replacement within a 10-year period because of too much "downtime" due to malfunctioning components or lack of sensitivity and inaccurate measurement capabilities.

No current mechanism exists within NIMH Extramural Programs to support the purchase of regular instrumentation, much less expensive high-technology equipment. Some institutions involved in mental health research have gained access to equipment and instrumentation through linkages with the NIH Division of Research Resources (DRR) Biomedical Research. However, eligibility for this shared instrumentation program is limited to institutions that receive BRS grant awards. A granting mechanism is needed at NIMH to provide for acquisition of instrumentation by its grantees, similar to the instrumentation grants programs initiated by several NIH Institutes.

The instrumentation required for contemporary neuroscience research ranges from positron emission tomography (PET) scanner and magnetic resonance spectroscopy and imaging equipment to smaller items required for the daily operation of a variety of biomedical laboratories. The ability to perform studies in molecular neurobiology and genetics requires dedicated equipment for peptide and DNA (oligonucleotide) sequencing, and synthesis equipment, high-speed ultra centrifuges, refrigerated centrifuges, ultra low temperature freezing, and tissue culture facilities. Analytical neurochemistry requires equipment ranging from high pressure liquid chromatography, liquid scintillation and gamma counters to gas chromatograph-mass spectrometers. Electrophysiological studies to investigate the patterns of electrical activity of the brain require highly specialized instrumentation including multichannel magnetoencephalograph equipment and minicomputers with graphics capabilities and with enhanced memory size and large disk storage capacity.

Similarly, neurobiology researchers need sophisticated computer-enhanced imaging of single nerve cells viewed with high resolution (to about one millionth of an inch) video-enhanced microscopy to visualize and quantify events that occur within the cell (such as increases in intracellular calcium), the formation of synapses, and their plasticity once formed. Modeling research also has equipment needs. These include computers for molecular modeling, for drug design (ligand-receptor modeling), and for modeling neural circuits.

The NAMHC recommends that NIMH establish:

- a **research instrumentation program** for grantees to update and expand their capabilities to perform state-of-the-art research in neuroscience. The award would be designed to meet the needs of the individual investigator or a group of investigators, and is not targeted toward shared resources for departmental, institutional, or regional needs. The intent is (a) to assist researchers in keeping pace with the rapid technological advances that have occurred in recent years in neuroscience and related disciplines, and (b) to foster the application of techniques and technologies from diverse disciplines to mental health research.

Funding for this program should be $10 million per year and should be represented in the budget as a line item apart from general research support.

Human Resources

A key factor in progress in the neurosciences over the next decade will be an adequate supply of trained scientists to explore opportunities created by new knowledge and technological advancements. In the last decade, the number of trainees and fellows receiving awards from ADAMHA each year decreased from 1,800 (in the early 1970s) to less than 1,000 in 1986, a 45-percent decline. In addition, the decrease in appropriations for research training and Research Scientists awards has not kept pace with inflation, increasing tuition costs, stipends, and other training expenses, so the current buying power of training funds is insufficient.

The rapid evolution in the neurosciences constantly creates demands for new types of specially trained researchers, without diminishing the continued need for existing specialties. The advantages of a strong, diverse research base are manifest in several recent advances from basic genetic studies to brain imaging. Over the next decade, input from many different disciplines will be essential in order to explore the power of new tools and to further advances on problems that neuroscience addresses.

The NAMHC recommends that NIMH develop:

- research training programs, through institutional training grants and fellowships, in molecular neurobiology including molecular

neurogenetics. Modern molecular biological techniques such as recombinant DNA (cloning) and transgenics (genetic engineering) have opened new possibilities for the study of the nervous system to forge fundamental insights into the ultimate basis for expression of mental illness. These methods can also be applied to clinical problems by addressing the issue of selective neuronal vulnerability to psychiatric disorders.

- support training programs in brain-imaging for radio-isotope chemists, psychiatrists, and computer scientists skilled in state-of-the-art techniques and approaches that have impact on problems relevant to mental health. New methods and theoretical frameworks are of highest priority. An important and rapidly developing dimension of both basic and clinical neuroscience involves emerging technologies (multinuclear magnetic resonance spectroscopy and imaging, near-infrared spectroscopy and imaging, magnetoencephalography, etc.) for anatomical and functional studies of the brain. The final aim is to obtain specific knowledge with high resolution noninvasive techniques about underlying mechanisms in the development and etiology of mental disorders.

- cross-disciplinary training to prepare researchers in the area of modeling neural circuits, which holds promise for developing new approaches to study how the brain might perform various mental processes such as perception, language, memory, problem solving, etc. The potential impact of neural modeling on mental research is tremendous. Unfortunately, there are few scientists who have the combined mathematical skills, background in physics, and the neurobiological intuition that is required.

It is essential to increase support for existing training programs now (FY 89) by approximately $3 million to make them commensurate with Initial Review Groups' (IRG) recommended amounts. A minimal increase of 10 new training programs per year will require an additional $2 million each year. The training initiatives outlined in the previous section will require additional resources for 40 fellowships per year amounting to $1 million each year. Research Scientist Awards (RSA) should be increased each year by 50, covering all categories of this program. In addition, NIMH should remove the current cap on salary support. This would require, on the average, $100,000 per award. Thus, in FY 89 the total requirement for continuation and new and competing RSAs would be $10.8 million.

Other Concerns

The NAMHC is also concerned with the facilities available to carry out the much needed and promising research pursuing the resolution of mental illnesses. These concerns relate to the availability of **imaging centers** for the study of psychiatric patients, and the availability of appropriate **animal facilities** for the maintenance and testing of special

populations such as mutant rodents, transgenic animals, and, most of all, primates. While there are obviously significant and meaningful homologies among the different animal species used in basic neuroscience research, there are also differences. In particular, primates offer the opportunity to examine and test significant brain/behavioral systems in the experimental animal most resembling humans. However, many of the major laboratories in this country are old and deteriorating, often making some experiments difficult to carry out and, in general, creating a poor work environment.

The NAMHC therefore recommends that NIMH:

- establish **brain imaging centers** with the capacity for positron emission tomograph, magnetic resonance imaging, and spectroscopy, as well as brain electrical activity mapping. The long-term goal should be to establish 10 such centers at an estimated annual cost of $5 million per center.

- establish a granting mechanism for the creation and maintenance of animal species, giving particular attention to the creation of appropriate **primate facilities** with sufficient support to purchase and maintain large enough colonies to do meaningful experiments. An estimated $10 million annually will be needed to initiate the establishment of this vitally important resource.

- provide matching funds for **laboratory renovations** and the creation of an appropriate work environment for scientists. In particular, emphasis should be given to those laboratories requiring upgraded facilities in order to work with the latest advances and methods in molecular biology, virology, and immunology. An estimated $10 million annually will be needed to initiate these vital laboratory renovations.

INTRAMURAL RESEARCH PROGRAM

Developmental Neurobiology

The structure and function of the brain is heavily influenced by developmental events during the critical periods of early life when the nervous system is undergoing rapid growth. Gene expression results from an interaction between information encoded in the gene and outside factors such as microorganisms, environmental chemicals, pharmacologic agents, and changes in maternal chemistry, including those induced by stress. Schizophrenia and manic-depressive illness represent developmental disorders with characteristic patterns of onset in late adolescence/early adulthood. An understanding of neuropsychiatric disorders of childhood, such as dyslexia and attention deficit disorder/hyperactivity, also hinge on knowledge of how the brain develops.

Such basic studies have recently led to a developmental theory of schizophrenia, derived from studies of brain development in primates, which proposed that a fixed, genetically influenced brain lesion interferes with normal maturation. The effects of the dormant damage are not usually apparent in childhood because the brain structures affected do not mature or become activated until the late teens or the early 20s.

A critical mass of basic investigation into the neuroanatomy and neurophysiology of development is assembling at the joint NIMH/NICHD animal research facility in Poolesville, MD. The most recent arrival is a highly regarded developmental neuroanatomist who studies the manner in which neurons interact to give rise to the complex organization of neuronal circuits. The research teams have recently discovered a permanent change in activity of the hormone oxytocin associated with the onset of motherhood in female rats. Studies have begun designed to unravel mechanisms linking behavioral set with measurable activity of prefrontal neurons in primates. Clinical brain imaging studies have implicated impairment of behavioral set in schizophrenia to the prefrontal cortex. Other studies are investigating interactions between the cortex and striatum as they relate to the activity of dopamine systems, which are known to be involved in schizophrenia and other mental disorders. Other animal studies modeling components of the illness are being planned within the Clinical Brain Disorders Branch at the NIMH William A. White (WAW) research facility.

It is precisely out of such strong basic research programs in the neurosciences that progress on understanding some of the most serious mental illnesses, such as schizophrenia, is most likely to come. Advances in clinical research on such illnesses are especially dependent on basic research in fields like developmental neurobiology because of the relatively primitive state of our knowledge about the underlying disease process in these disorders.

The NAMHC recommends that the NIMH Intramural Research Program:

- provide the necessary support to attract top-flight investigations into intramural developmental neurobiology studies in Poolesville and at the WAW Building.

Staffing and other object costs would be approximately $709,000.

Molecular Biology, Molecular Genetics, and Gene Mapping

Molecular biological methodologies hold special promise for understanding the brain. By transplanting genetic material, animals with novel genes can be "mass produced" for physiological,

pharmacological, and behavioral studies. The effect of placing a neurotransmitter in nerve cells that do not normally make it can be investigated. Fundamental questions about how the brain, in all its complexity, grows from a small tube of primitive, undifferentiated cells can be pursued. Molecular genetics can also be applied to clinical problems. The causes of diseases that have major genetic components, including depression and schizophrenia, can be better characterized by studying patients' DNA and through other molecular approaches.

While the scientific opportunities in this rapidly advancing area are virtually limitless, intramural efforts remain constrained by a need for expensive sequencing machines and other equipment and the resources required to recruit enough investigators skilled in these methodologies. For example, only one operational gene sequencing machine and two protein sequencing machines are currently available for all the Institutes at the National Institutes of Health.

Intramural molecular geneticists have recently discovered the mutations within a defective gene responsible for Gaucher's disease and cloned and sequenced the chemical structures of the gene for the enzymes that make dopamine and serotonin. They are also hot on the trail of a possible gene locus for the schizophrenia spectrum disorders and are testing newly developed genetic probes in cultured cell lines from manic-depressive patients. Anticipating the eventual mapping of the human genome, intramural investigators are building an infrastructure of cultured cells and pedigree information from families affected by serious mental illness.

No other approaches available to modern science offer more promise for rapidly discovering the underlying illness processes in serious mental disorders than molecular biology/genetics techniques.

The NAMHC recommends that the NIMH Intramural Research Program:

- make the necessary manpower and monetary resources available to follow up the rapidly expanding opportunities at the interface of neuroscience and molecular biology.

Neuroscience/Primate Research Laboratories

The NIH campus currently has no accreditable primate research facility and no integrated facility where NIMH and its sister neuroscience Institutes (NICHD and NINCDS) can efficiently conduct the studies in these animals so vitally important to understanding the brain. Neuroscience facilities of the three Institutes are scattered—as far away as Poolesville or Frederick—resulting in fractionated, inefficient programs. NIMH operates a satellite facility in the William A. White Building at Saint Elizabeths Hospital that conducts extremely valuable research on schizophrenia, dementia, and related neurosciences, including primate

studies. However, the setting has made it difficult to recruit scientists, and the 1920s-era building requires extensive renovations.

In FY 87, the Congress appropriated $4.4 million to design a multi-institute neuroscience research center (Building 49), containing state-of-the-art primate facilities, to be located south of the NIH Clinical Center, which would be shared by the three Institutes. Building 49 would allow for acceleration and integration of critical studies on the brain. The momentum in brain research is now extraordinary, with an unprecedented window of opportunity created by the advent of modern techniques in molecular biology, immunology, and cell biology.

NIMH research is focused on fundamental studies of the anatomy and biology of the brain and its specific neurotransmitters and receptors, particularly as they relate to the complex patterns of behavior involved in serious mental illnesses such as schizophrenia and manic-depressive illness. An understanding of these abnormalities, at the molecular level, should lead to more effective therapy and possibly to prevention. Since all brain research represents a continuum, bringing the programs in this area together under one roof will greatly enhance productivity while yielding great economies of scale through eliminating the need for duplication of support services required at the various off-site locations, such as the WAW building.

The NAMHC recommends that the NIMH Intramural Research Program:

- realize and accelerate the intent of Congress through the actual construction of Building 49, beginning in 1989, so that it will be ready for occupancy by early 1991.

Neurovirology/Neuroimmunology Initiative

Interdisciplinary teams of intramural investigators have recently made important discoveries about how the AIDS virus attacks brain cells, cognitive side effects of cancer immunotherapy, possible viral links to schizophrenia, and immune system reactions to experimentally induced stress. These findings suggest profound regulatory interactions between the brain, immune, and endocrine systems and provide leads to mechanisms by which immune system disorders produce behavioral disturbances and vice versa. Finding that these systems contain shared molecular components, peptide messenger chemicals, and receptors opens up a vast new potential for understanding possible autoimmune and viral components of neuropsychiatric disorders, such as schizophrenia.

Following the discovery that peptide T, an analog of a brain peptide messenger chemical, can inhibit entry of the AIDS virus into brain and immune system cells, intramural scientists initiated clinical trials of

this experimental drug in AIDS patients in collaboration with the University of Southern California. Work on the drug's mechanisms of action and potential as the basis for an AIDS vaccine continues within the Clinical Neuroscience Branch. Other groups are following up findings that environmental factors such as light and various stressors exert profound effects on immune system function. An immunologist from the Centers for Disease Control who recently joined the William A. White facility is investigating evidence that brain-specific strains of viruses may be associated with AIDS dementia.

Mechanisms involved in neuroimmunology/neurovirology are of direct relevance to many major public health problems. Following up the exciting research leads in this area promises improved understanding of as yet poorly understood disorders, such as schizophrenia, as well as possible new treatments for such monumental challenges as AIDS.

The NAMHC recommends that the NIMH Intramural Research Program:

- expand its intramural efforts in psychoimmunology and neurovirology to focus on two priority initiatives: the creation of a core psychoimmunology group comprising several key neuroscientists, strengthened by the recruitment of three experienced immunologists; and expansion of clinical psychoimmunology, focusing on AIDS patients, including PET and MRI studies.
- in collaboration with NIAID, expanded studies of neuropsychological changes should be integrated with brain imaging studies in AIDS patients undergoing experimental treatments. Key to this effort will be the availability of longitudinal measures of both immunologic and neuroendocrine function. This new effort will require modest expansion of the consultation/ liaison program run by the NIMH on behalf of the NIH Institutes.
- establish a virology unit within the intramural program to expand the capacity to evaluate new antivirals;
- capitalize on receptor research and other approaches familiar to psychopharmacology.

This will require investment in new hardware, such as gene sequencers (about $100,000 apiece), protein sequencers ($160,000), and DNA extractors ($50,000), and other resources necessary to attract high caliber molecular biologists into brain research.

Neurobiology of Learning and Memory

As neuroscience techniques are perfected at the molecular level, it is increasingly feasible to mount studies aimed at unraveling basic mechanisms of learning and memory. Advances along this frontier would be of great basic and clinical interest since memory and learning

mechanisms may be fundamental to many psychiatric disorders, including Alzheimers Disease, attention deficit disorder, schizophrenia, and depression. Related cognitive studies of memory should also be expanded.

A new thrust in the area of molecular mechanisms would complement ongoing research in primates on the behavioral neuroanatomy of memory within the Laboratory of Neuropsychology and burgeoning cognitive and brain imaging studies underway in collaboration with clinical investigations of the various disorders. Gaining an understanding of how representations of stimuli are transmitted and stored within neurons and what role specific neurotransmitters and receptor proteins play in this process could ultimately lead to the engineering of specific-acting memory-enhancing drugs and other interventions for clinical populations. It could also illuminate much about the pathophysiology of disorders characterized by memory or learning impairments.

The NAMHC recommends that the NIMH Intramural Research Program:

- mount an initiative on the neurobiology of learning and memory within the Laboratories of Cell Biology, Neuropsychology, and Clinical Science and within the Biological Psychiatry and Clinical Brain Disorders Branches.

Ten positions and $300,000 in other object funds would be required to adequately support these initiatives.

☆ U.S. GOVERNMENT PRINTING OFFICE: 1989 - 241-280 - 814/93692

DHHS Publication No. (ADM) 89-1580
Alcohol, Drug Abuse, and Mental Health Administration
Printed 1988, Reprinted 1989